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EPIDEMIC POLIOMYELITIS

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THE disease poliomyelitis is endemic in many parts of the United States throughout the year, but epidemic periods usually are evident by June or July, the peak being in August or September with a beginning decline by October. In the warmer climates of the United States, the disease may show an upward swing as early as April, as was the case in the Los Angeles area during the 1943 epidemic. This general cycle of endemicity and epidemic peaks is repeated regularly with moderate to severe epidemics being prevalent every four to six years, with a general regional variation in the United States.¹

The diseases transmitted by direct contact, such as meningococcus meningitis, whooping cough, measles, and mumps are more prevalent in the late fall, winter, and spring months. Such disease agents are more frequently spread from person to person by nasopharyngeal droplets. In contrast, poliomyelitis is a summer or late summer and early fall disease, with peaks more akin to those of enteric diseases or to the morbidity of insect born diseases. Enteric diseases, such as typhoid fever and dysentery, may, however, become epidemic in any month if a water or food supply is contaminated, and these epidemic peaks are frequently reached with explosive suddenness. A recent fly-borne epidemic of *Shigella paradysenteriae* Boyd 88 was reported by Kulins and Anderson.² No flies were observed in the bivouac area prior to September 1. Flies began to appear and as the epidemic increased, great numbers were present. A total of 1,557 cases were reported from September 1 to the first week in October. The morbidity decreased with a decrease in fly population. The specific organisms producing the disease were isolated from several samples of flies trapped near the encampment.

Poliomyelitis cases, on the other hand, generally increase more gradually, the epidemic peak coming in late August or September, depending upon the area. In the poliomyelitis epidemic of 1943, in California, the following monthly cases were reported: April, 27; May, 43; June, 181; July, 380; August, 506; September, 590; October, 269; November, 204; and December, 69. There is then

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a fairly abrupt falling off of cases in October with only a few appearing as late as December.

Poliomyelitis is also characterized, in many instances, by sporadic and isolated cases, with several spotted cases in various suburban as well as urban areas during an epidemic. Likewise, there is a paucity of cases among closely associated groups, such as schools, orphan homes, or nurseries. It seems, therefore, that if this disease were strictly a contact disease there should be more cases in these latter groups as is the case with strictly contact diseases.

Various opinions have been advanced as to the reason for the seasonal incidence of epidemic poliomyelitis, with suggestions as to the mode of spread of the disease. Direct contact spread via the nasopharynx has been suggested by Flexner,³ Schultz and Gebhardt,⁴ Aycock,⁵ and others. Water supplies have been suggested as a vehicle by which virus may be spread (Kling,⁶ Toomey,⁷ and others). A few small epidemics have been proved to have been milk-borne (Knapp, Godfrey, and Aycock,⁸ Aycock⁹). Food contaminated with virus has also been suggested as a possible means by which the disease agent gains entrance to the body (Toomey and August,¹⁰ Toomey,^{11, 13} and Barber¹²).

Virus has been isolated from stools of patients with active cases of the disease and convalescents as well as from the stools of carriers who have had no evidence of the disease clinically.¹⁴⁻¹⁸ The virus has also been isolated from sewage during nearly every month of the year.¹⁹⁻²¹

The possibility of insect transmission of the virus has gained momentum in the past few years, since the virus has been isolated from several species of flies (Paul and associates,²² Sabin and Ward,²³ Trask and associates,²⁴ Sabin and Ward²⁵).

EPIDEMIOLOGICAL SURVEY

Previous to 1943, the greatest number of cases reported in the State of Utah was 109 in 1939, but in 1943 there were 400 cases in the State.

During late August and early September, 1943, the disease reached epidemic proportions, with 43 cases in August and 211 cases during September. A survey was therefore begun in an attempt to find, if possible, something in common with all or a high percentage of the cases of the disease. The following possibilities were considered as means by which the virus may be spread from one individual to another: direct contacts, water supplies, swimming pools, insect bites, milk supplies, and food supplies.

CONTACTS

Actual contacts with diseased patients were very few, and patients developing the disease after exposure from five to twenty-five days with a known case of poliomyelitis showed only 33 cases of 241 surveyed, or 13.6 per cent, possible direct contact infections.

The Salt Lake City Public Schools were to have started their fall term Sept. 8, 1943, but due to the poliomyelitis epidemic students from kindergarten to the sixth grade were not allowed to attend school. Students from the seventh grade through high school attended school September 8, 9, and 10. The complete school system was then ordered closed until September 27.

During the month of August, there was a total of six cases of poliomyelitis in Salt Lake City in children from the age of 6 to 17 years. This was during the time when no school was in session. During September while schools were closed, there were thirty-five cases of poliomyelitis in the same age groups, 6 to 17 years. During October there were twelve cases of poliomyelitis in Salt Lake City in this age group or a decided decline in the number of cases after school reopened. These figures, therefore, correlate the epidemic trend in the State, irrespective of school association. (See Graph 1.)

After reopening the schools,* September 27, 29,099 students returned to school. By October 1, 30,351 students had returned; by October 20, 31,243 students had returned. It was, therefore, not until this latter date that the total enrollment had returned to school. Many parents kept their children from school after reopening, fearing that they might contract the disease.

From the data given, it would appear that children are just as safe in school as they are out of school. It also fails to reveal any increase in the number of cases of the disease with a reopening of school, with "contacts" greatly increased in the schoolroom as well as on the playground.

Two isolated cases suggested that means other than direct contact may play a role in the spread of the disease. One case, J. J. W., a 3½-year-old girl, developed the disease at a sheep camp, seventy miles from the nearest inhabitant. This child came to town during the summer only about one day each month with the family to purchase supplies. The family lives in this town during the winter and spring months. This child came to their home and remained in town one day, twenty-seven days previous to developing the disease. There were no poliomyelitis cases during 1943 in the town where the family normally lived, and to the knowledge of the mother, the child had contacted no one with even a suspicion of any disease. Foodstuffs, including fresh fruits and vegetables, were taken back with them to the camp as supplies. The only inhabitants of the camp were the father, mother, and the child.

The other case, G. A., a 13-month old male, lived in a small town of 473 inhabitants. This child went to the outskirts of a city 101 miles distant, with his mother, two weeks previous to his developing poliomyelitis. They contacted no one; the mother picked apples from an orchard and then came home. The farm from which the apples were obtained was located in a fairly extensive epidemic area. None of three sisters, who remained at home, ranging in age from 5 to 11 years, developed any illness whatsoever. The three sisters did not eat any unwashed fruits except peeled ones, while the baby, on two known occasions, had played with and had bitten into several unwashed apples obtained from the epidemic area. There were no other cases of poliomyelitis in this town or even in neighboring towns, fifty or more miles distant.

The only possible thing in common in these two isolated cases was fresh fruit—"apples." Both children had nibbled at or had eaten unwashed, unpeeled apples, from one to two weeks previous to developing the disease.

*Arthur E. Arnesen, Supervisor of Curriculum and Research, The Board of Education of Salt Lake City, Utah: Personal communication.

WATER SUPPLIES

The diversity of water supplies, including springs, dug wells, drilled wells, and artesian wells, suggested that water supplies were not incriminated in the spread of the virus during this epidemic. Even the water supply of Salt Lake City is not from one single source, but from several sources, with separate storage reservoirs and distributing systems for different areas of the city. Cases of the disease were too scattered to consider any given water supply as a source of virus.

MILK SUPPLIES

Milk supplies for the various villages, towns, and cities came from variable sources, and no direct connection of cases of the disease with any single or multiple milk sources could be traced. The family cow, neighbors' cows, milk from first-class dairies, and from well-regulated processing and pasteurizing plants, all supplied milk, and no correlation between cases and milk supplies could be elicited in 241 cases of the disease surveyed.

SWIMMING POOLS

Of 241 interviews with persons having poliomyelitis, eleven, or 4.1 per cent, had been in swimming from five days to two weeks previous to developing the disease. The swimming pools varied from creeks, irrigation ditches, and farm ponds to regulation swimming pools. The variable areas of these water sources for swimming failed to reveal any connection of disease spread by such contact.

INSECT BITES

Of 241 cases surveyed, 105 persons, or 43.5 per cent, gave histories of being bitten by mosquitoes or flies from five days to two weeks or more before developing the disease. However, in over one hundred normal persons surveyed in the same areas, about the same percentage revealed mosquito or fly bites. These included normal sisters, brothers, mothers, and fathers of patients with poliomyelitis, as well as children with no family history of the disease.

FOODSTUFFS

No attempt was made to determine the kinds of cooked or prepared foods eaten by the children who developed poliomyelitis. Only raw, uncooked, and unwashed types of foodstuffs were considered as a possible source of virus, since heating to 60° C. for a few minutes destroys the virus. Therefore, the field was narrowed to fresh uncooked foodstuffs.

In many instances parents were insistent that all fresh fruits and vegetables eaten by the child who had developed the disease were washed or peeled. On closer questioning, nearly all the parents admitted that the child had eaten unwashed or unpeeled fresh fruits or vegetables. In other instances, if the child were old enough to question, he admitted eating raw unwashed fruits or vegetables, even though previously the parents insisted all foodstuffs of this nature had been washed or peeled. Pride of parents often was a stumbling block, and an "I don't remember" answer was frequent.

Of a total of 206 cases of poliomyelitis surveyed, 192 persons, or 93.2 per cent, had eaten unwashed or unpeeled fresh fruits one to two weeks or more previous to developing the disease. Among the fresh fruits more commonly eaten were apples, peaches, and pears. Less commonly eaten were cherries, grapes, apricots, and plums. Strawberries were eaten unwashed only rarely, due primarily to the high cost and to the fact that this foodstuff was kept out of reach of children prior to preparation for eating.

Of this same group (206 cases), 140, or 67.9 per cent, also ate fresh, unwashed or unpeeled vegetables. Tomatoes led the list of such vegetables. Raw celery and carrots were less frequently eaten by the persons surveyed.

A combination of the two categories, unwashed or unpeeled fresh fruits and vegetables, shows that 206 out of 206, or 100 per cent, of the patients with poliomyelitis in the survey had eaten these foods one to two weeks or more prior to developing the disease.

The only foods found in common in all of the cases of the survey were therefore, fresh fruits and vegetables. This in itself would not lend too much evidence as a possible means of spread of the virus if other data failed to dovetail, since it is frequently a common practice for children to eat raw unwashed fruits and vegetables. Such data, however, appear to fit into the jigsaw puzzle of epidemic poliomyelitis.

COMPARISON OF FRUIT AND VEGETABLE HARVEST WITH PEAK POLIOMYELITIS CASES

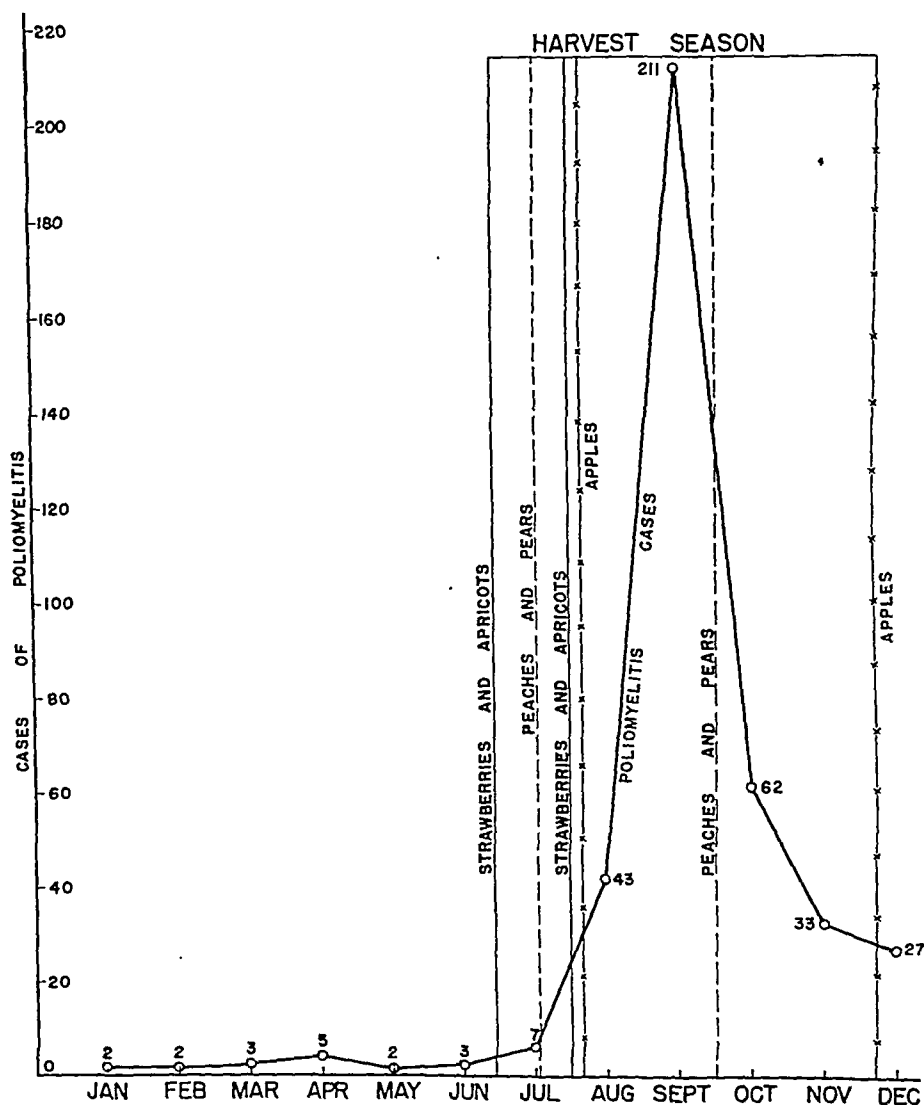
It has been previously suggested by Toomey^{10, 13} that epidemic poliomyelitis may bear some relationship to the peak harvest of fresh fruits. He also suggested that the incidence of flies was greater during the harvest peak, particularly during the fruit seasons. No explanation was offered, however, as to how fruits may be a transfer agent for this virus.

From the data collected, it is noted that peach, pear, and apple production peaks, particularly,^{26, 27} closely parallel epidemic poliomyelitis case peaks (Graph 1). From this graph it is shown that such edible fruits as strawberries and apricots in Utah begin to ripen in June and are usually off the market by the end of July or the first part of August. The number of cases of poliomyelitis in June, 1943, was 3; in July, 7. In Utah, beginning the middle of July, peaches and pears begin to ripen with peak ripening periods in August, but continue through September. Poliomyelitis cases in August were 43. Apple ripening in Utah begins in early August, continuing through November, with peak ripening in September and through October. The tomato season is from August through October, with a September peak production. The total cases of poliomyelitis in Utah in September, 1943, was 211; October, 62; November, 33; December, 27. In other states, during 1943, this same trend is evident.

In the State of New York, in 1943, the number of cases rose from 3 in May to 20 in June and then 36 in July. In August 132 cases were reported and in September 300, the case peaks paralleling harvest peaks.²⁶⁻²⁸ Strawberries and cherries both begin to ripen in June, the former carrying through the latter part of July with cherries extending beyond the end of August. Peaches begin

to ripen the latter part of July and the first week in August, continuing through October. Pears and apples begin to ripen the latter part of August and the first week of September and carry through early fall. Graph 2 shows the relationship.

POLIOMYELITIS CASES AND FRUIT HARVEST UTAH 1943

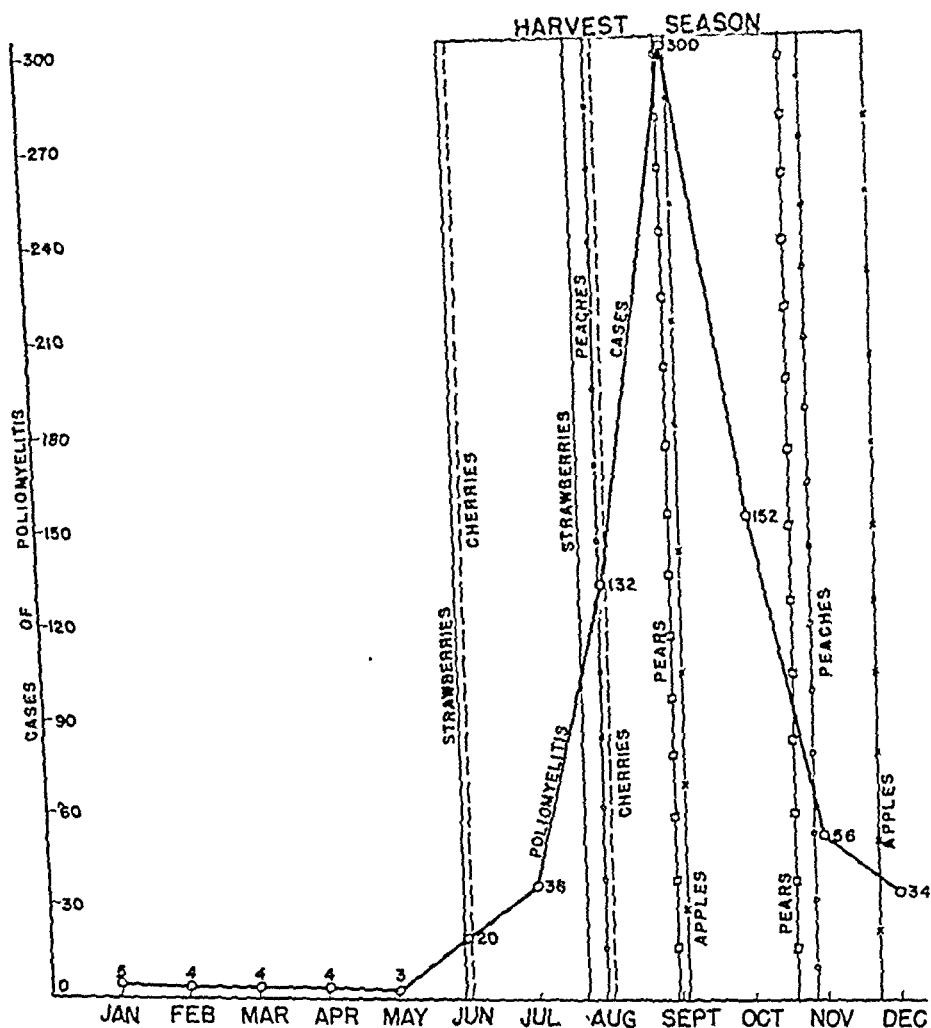


Graph 1.

In California,^{26, 27} if fresh fruits and vegetables were in some way responsible for the carriage and dissemination of virus, one would expect an earlier appearance of an epidemic. Likewise, a greater number of cases should be maintained at or near the peak than in states with a shorter and less varied fruit and

vegetable season. Graph 3 shows this relationship. The epidemic in California was suggested as early as April, with 27 cases; in May, 43 cases were reported; June, 181; July 380 (Contrast this with 36 cases in July in the State of New York); August, 506; September, 590; October, 269; November, 201; and December, 69. What relationship, then, does the spread of poliomyelitis virus have

POLIOMYELITIS CASES AND FRUIT HARVEST NEW YORK 1943



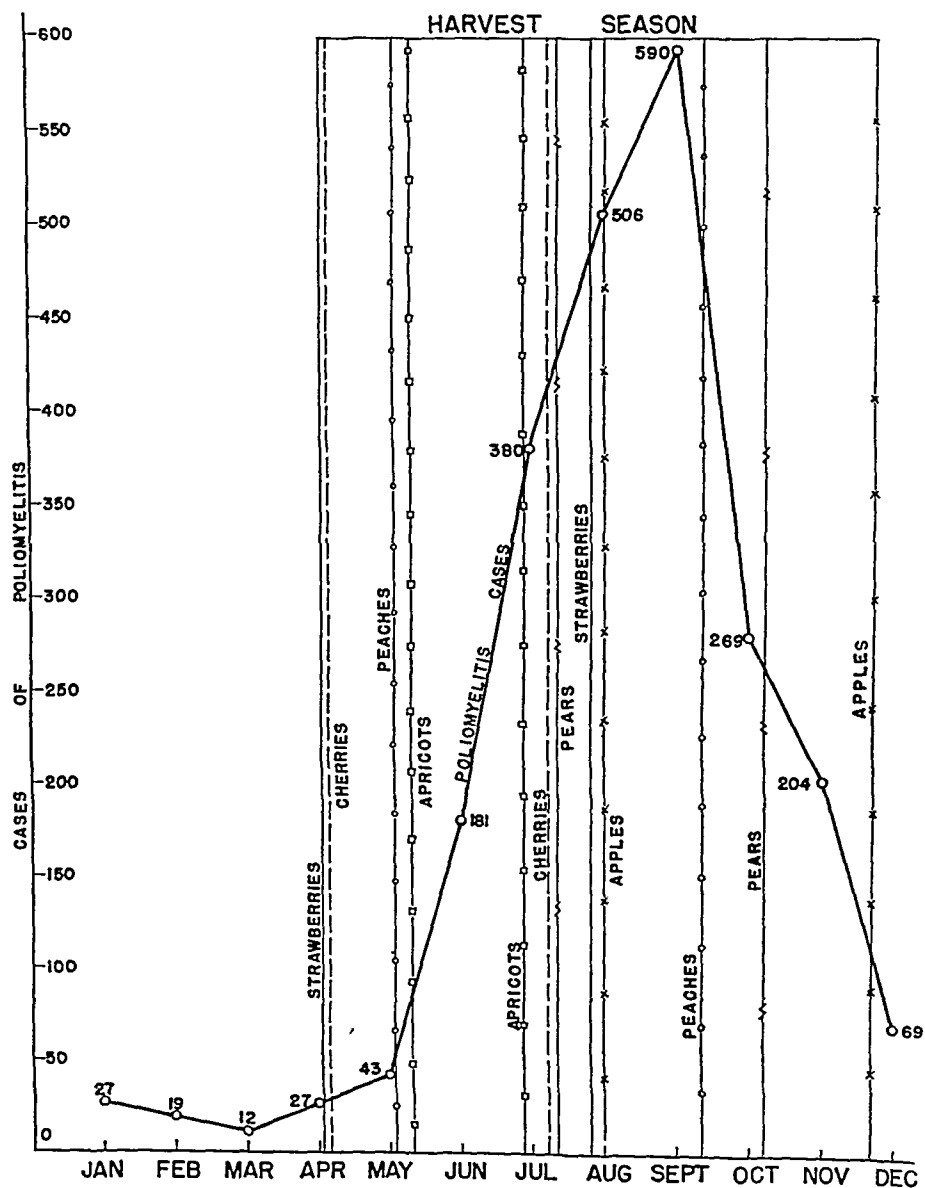
Graph 2.

to fruit or vegetables? How do such edible foods become contaminated? Why should children be affected more frequently with this disease?

It has already been shown by several investigators that certain flies may harbor the virus of poliomyelitis. It has also been shown that sewage is an

excellent source of the virus. Thus, flies obtaining virus from sewage might easily deposit fecal material containing the virus on fruits and vegetables. Fresh fruits and vegetables are invariably exposed to flies both in the field and on vegetable and fruit stands as well as on peddlers' trucks. Virus containing

POLIOMYELITIS CASES AND FRUIT HARVEST CALIFORNIA 1943



Graph 3.

fly feces deposited on such foodstuffs would, therefore, offer a "virus source" to be ingested by susceptible individuals. If such foodstuffs are unwashed, virus may be taken into the mouth when these foods are eaten. Passage of "natural sewage or fecal virus" through flies may enhance its virulence* or increase its quantity. If the fly population is high and ample sewage virus available, the probability of more flies being carriers of virus seems possible.

It is conceivable that of a given group of foodstuffs, only a few units may be contaminated, or, on the other hand, if many units are contaminated, the virus may be more widely distributed. In the former, only a single unit may have been contaminated by fly feces, and thus only one person of a family unit may obtain the virus. Since children from 2 to 15 years of age are not usually particular about "washing" such raw foodstuffs, this age group would be more likely to become infected. Also the more active child is more prone to get into such foods unobserved. Likewise, if subinfecting quantities of virus are deposited, the person ingesting the virus may well have no effects or at the most only very mild, subclinical symptoms, resulting in an immunity. If many units of foodstuffs are contaminated by fly feces virus, many cases of the disease will be evident, if sufficient virus is deposited on the foodstuff to produce infection. Thus, if a given family obtains such contaminated foodstuffs, more than one family member, if susceptible, will develop the disease, or harbor the virus in their nasopharynx or in the feces. Multiple cases in such a family would, therefore, develop the disease or symptoms at or about the same time. This fact is suggested by a study of multiple cases in families.

MULTIPLE CASES IN FAMILIES

From the data presented in Table I, 45 multiple cases in 20 families show that the development of the disease was, in 32 of the cases, on the same day or within zero to five days after the brother or sister developed poliomyelitis. The longest interval between family cases was 61 days; the shortest interval between family cases was zero days (12 cases). It is, therefore, highly probable that the majority of these multiple cases obtained their infection from a common source and at about the same time.

It is suggested that members of a given family unit, mother, father, and siblings, may all harbor the virus of poliomyelitis in their feces at or about the same time, but only one member may exhibit symptoms of the disease.²⁰ The virus is, therefore, probably more widely distributed in family groups than was previously thought. The family unit, therefore, undoubtedly obtains the virus from a common source and the probability of "contact" of all members with another human case or carrier of the virus at the same time does not seem entirely reasonable.

PREVALENCE OF FLIES

Many species of flies were prevalent in Utah in 1943 in fairly great numbers, and during August and September swarms of flies were in evidence. It was not difficult to trap several hundred of several different species in a single day.

*In this laboratory, it has been demonstrated that the VI antigen of *Eberthella typhosa* increases slightly on fly passage.

TABLE I. MULTIPLE CASES OF POLIOMYELITIS IN FAMILIES IN UTAH, 1943

FAMILY	CASES PER FAMILY (NO.)	DATES OF ONSET	INTERVAL IN DAYS BETWEEN CASES IN SAME FAMILY
1	2	July 15	
		July 15	0
2	2	Aug. 1	
		Aug. 13	12
3	2	Aug. 13	
		Aug. 20	7
4	3	Aug. 16	
		Aug. 20	4
		Aug. 23	3 (7)*
5	2	Aug. 24	
		Aug. 24	0
6	4	Aug. 29 (two)	0 (two)
		Aug. 31 (two)	2 (two)
7	3	Aug. 27	
		Sept. 1	4
		Sept. 7	6 (11)*
8	2	Sept. 2	
		Sept. 3	1
9	2	Aug. 3	
		Sept. 9	36
10	3	Sept. 3	
		Sept. 8	5
		Nov. 8	61
11	2	Sept. 4	
		Sept. 11	7
12	2	Sept. 6	
		Sept. 8	2
13	2	Sept. 10	
		Sept. 12	2
14	2	Sept. 10	
		Sept. 14	4
15	2	Sept. 14	
		Sept. 14	0
16	2	Sept. 15	
		Sept. 15	0
17	2	Oct. 4	
		Oct. 4	0
18	2	Oct. 15	
		Oct. 20	5
19	2	Oct. 16	
		Nov. 11	26
20	2	Nov. 25	
		Nov. 26	1

*Longest interval in days between first and last case where there were more than two cases per family.

Likewise, hand-netting produced an abundant catch. Flies became numerous the latter part of July and continued to be fairly numerous to the middle of November. A few *Phormia regina* were trapped in lecture rooms and laboratories, during the winter of 1943-1944, at which time the outside temperature ranged from -1 to +10 degrees F.

The following species of flies were trapped* and identified:† *Phormia regina*,‡ *Lucilia sericata*, *Calliphora erythrocephala*, *Fannia canicularis*, *Fannia scalaris*, *Musca domestica*, and *Muscina stabulans*. *Fannia canicularis* were

*Flies were trapped or hand-netted and a preliminary identification was made by Mr. Dan Oniki, Department of Biology, University of Utah.

†Final identification of flies was made by Dr. David T. Jones, Associate Professor, Department of Biology, University of Utah.

‡In a single experiment laboratory bred *Phormia regina* flies fed "virus bearing" sewage, possessed the virus of poliomyelitis in the feces, collected (pooled) ten to fifteen days after feeding. Other similar experiments have thus far been negative for virus.

trapped both inside and outside of buildings and as the usual incidence, males predominated inside. However, outside catches revealed a fairly high percentage of female *F. canicularis* in 1943.

In 1944, however, when a total of only twenty-four cases of poliomyelitis was reported in Utah, flies were comparatively scarce. It was difficult to trap a hundred flies, and this took several days unless baited areas were used such as garbage cans, decayed meat, or other similar places. It is also of interest to note that during 1944 the male to female ratio of *F. canicularis*, trapped out of doors, was 293 to 2. If flies are responsible for the dissemination of virus, the female may, for some reason, play a more important role than the male. The quantity of available food influences the ratio of males to females, and with abundant food females are about 2 to 1 more prevalent (Hermes²⁰).

In one small peach orchard located in a small town and surveyed in September, 1943, thousands of flies of several species were swarming about the fallen fruit. Likewise, in the same month, a small apple orchard ten miles distant from the peach orchard was found to be literally swarming with flies. Both orchards were frequented by many children ranging from 3 to 15 years of age. Eight cases of poliomyelitis were near these areas. These same orchards, in 1944, revealed very few flies during either August or September. In a home near (two hundred yards) this apple orchard, three children in one family developed the disease, all three having frequented this orchard and eaten fallen unwashed fruit, one to two weeks or more previous to developing poliomyelitis. No known contacts with cases of poliomyelitis could be traced in this group of cases.

RELATIONSHIP OF OPEN PRIVIES AND DRAINS TO POLIOMYELITIS CASES

In one city of 5,214 inhabitants, surveyed²¹ for open privies and drains, it was found that in the eastern section, sewage facilities were undeveloped. There were thirty-two open privies and drains from waste disposal units. In this section, there have been thirteen cases of poliomyelitis. In the southern section outside the city limits, where no sewage system exists, five cases of poliomyelitis have been reported. In the north and west sections, which have adequate sewage systems, no cases have been reported. Several small orchards are located near these areas.

In another city of 2,733 inhabitants, 13 cases of poliomyelitis developed during 1943. This is a morbidity rate of 468, which is nearly eight times the State morbidity rate of 61.5 for the same year. The sewage disposal units in this city consist of open privies, cesspools, and septic tanks. Open ditches containing raw sewage are prevalent.

Great swarms of flies were present in this area in August, September, and October, 1943, but flies were quite scarce during the same period in 1944. Traps baited with decaying meat, fruit, and human feces failed to net more than forty to fifty flies in several five-day periods of collection in the above locality during the above three months in 1944.

DISCUSSION

The data presented in Table I point to other means than contact as the mode of spread of this disease. Twelve multiple cases of poliomyelitis developed in six families on the same day; twenty multiple cases developed from one to

five days after onset of the disease in a brother or sister and ten of these cases developed within two days of that of the siblings. Of a total of forty-five multiple cases in families, thirty-two developed in less than the generally accepted incubation period of from seven to fourteen days after exposure, if we consider the brother or sister to expose another member of the family. In one family with four cases, two children developed the disease the same day and two developed the disease two days after. Two other children, who had played with those in the family with four multiple cases and had eaten of the same unwashed peaches, apples, and pears on Aug. 17 and 18, 1943, developed the disease August 31 and September 1, respectively, or about the same time that the multiple cases of the disease (four in one family) had developed. This data therefore suggests that the majority of these patients were exposed to the virus at about the same time and probably from the same source. No direct contacts with any known cases of poliomyelitis and the multiple cases could be traced, except the family unit and the two cited cases of patients who developed the disease at the same time as the four children in the other family.

This is in contrast with multiple cases in families having a well-known contact disease such as measles, mumps, or chicken pox, where a brother or sister generally develops the disease after the regular incubation periods, when secondary cases in families develop.

Possible common virus sources for these multiple cases of poliomyelitis in families could be virus contaminated foodstuff, since all members of a given family unit usually eat the same kind of food.

Peak fruit and vegetable production and highest fly incidence correlate the peak period of poliomyelitis cases and the evidence presented that 100 per cent of the persons in the cases surveyed had eaten unwashed or unpeeled fresh fruits and vegetables from one to two or more weeks prior to developing poliomyelitis, suggests that foods may play a role in the dissemination of the virus. Ample virus source could well be represented in areas of faulty sewage disposal and with swarms of flies present, virus-to-fly-to-food-to-patient seems to be in the realm of probability. Such foods that may be contaminated with the virus find their way into many different areas, including remote and isolated places, which would account for isolated and sporadic cases of the disease.

It is suggested, therefore, that poliomyelitis is an accidental disease of the "filth borne" group of diseases; that "virus contaminated food" may play a very active role in the spread of this disease. The limitations of spread of the virus would be dependent on fly population, source of virus for flies, and an adequate source of fresh foods, such as fruits and vegetables, as well as other foods that may be eaten uncooked. Also that such foods be convenient to populated areas in order for virus, that may be deposited, to survive for a sufficiently long enough time to be ingested by susceptible individuals.

Definite proof of the spread of virus of poliomyelitis by means of contaminated food rests on actually isolating the virus from fresh foodstuffs and demonstrating that flies may contaminate such foods by depositing virus thereon. Such proof has been suggested by Ward and associates³² since they were able to isolate the virus from bananas contaminated by flies.

SUMMARY

1. Multiple cases of poliomyelitis in families show that the majority of the cases developed at the same time. Also that in these multiple cases the children probably obtained the virus at the same time and from the same source, suggesting means other than contact as the mode of spread.
2. Fresh unwashed or unpeeled fruits and vegetables were eaten in 206 of the 206 cases of poliomyelitis surveyed.
3. Direct contact was traced in only 13.6 per cent of the 241 cases surveyed.
4. No evidence was found that water supplies, milk supplies, or swimming pools were means by which the disease was disseminated.
5. Bites of insects, such as flies and mosquitoes, suggests a possible means of virus spread.
6. Closing of schools during the epidemic failed to reduce the incidence of the disease among the school age group.

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RESISTANCE OF COTTON RATS TO THE VIRUS OF POLIOMYELITIS

AS AFFECTED BY INTAKE OF VITAMIN A, PARTIAL INANITION AND SEX

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A NUMBER of clinical¹ and of experimental² studies have indicated that partial inanition and/or vitamin intake might influence susceptibility to the virus of poliomyelitis. Our own experience³ has been that neither sex, partial inanition, nor the avitaminoses B and D significantly affect the susceptibility of cotton rats to the Armstrong-Lansing strain of the virus.

Since the virus of poliomyelitis undoubtedly enters the host through one or more epithelial surfaces, and since the physiologic state of epithelia is, among other factors, dependent upon an adequate intake of vitamin A,⁴ it was thought advisable to study the possible effects of avitaminosis-A on the susceptibility of the host to the virus.

The present communication records the results of a number of experiments which were designed to test the effects of Vitamin A-free diets, of partial inanition and of sex on the susceptibility and on certain immunologic responses of cotton rats to the Armstrong-Lansing strain of the virus of poliomyelitis.

MATERIALS

The Armstrong-Lansing strain of the poliomyelitis virus which has been adapted to the cotton rat was employed in these studies. Unfiltered, lightly centrifuged stock suspensions of the virus were prepared exclusively from the brain stems and spinal cords of paralyzed cotton rats. These nervous tissues had been stored in buffered glycerine at 5° C. for a period of time not exceeding two months. During the course of this investigation, samples of the stock virus suspensions were injected in large quantities (intracerebrally, intranasally, intraperitoneally, and subcutaneously) into albino rats, wild rats, guinea pigs, Syrian hamsters, Swiss mice, and *Macacus rhesus* monkeys. We were unable to reproduce the disease in albino rats, wild rats, and guinea pigs. On the other hand, the disease was consistently reproduced by intracerebral inoculations of the virus into Swiss mice and *Macacus rhesus* monkeys. Suspensions of the spinal cords of the mice and of the monkeys repeatedly produced paralytic anterior poliomyelitis when injected intracerebrally into cotton rats. On three occasions a condition resembling anterior poliomyelitis developed in hamsters which had been inoculated with the virus. Although flaccid paralysis was observed in the animals, and microscopic sections of their spinal cords showed poliomyelitic lesions, we were unable to serially pass the virus beyond the second generation.

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The cotton rats employed in this study were obtained from the Michigan Department of Health Laboratories.

The basic diet of the control animals was composed of a mixture of natural foods as follows: cane molasses, peanut oil meal, soy bean oil meal, animal liver meal, fish meal, meat scraps, condensed buttermilk, corn gluten, wheat bran, wheat flour middlings, ground whole oats, ground whole yellow corn, ground hulled barley, ground whole wheat, whole milk powder, alfalfa leaf meal, A and D feeding oil (a Rockland Farms product), steamed bone meal, salt, and precipitated chalk.

The vitamin A-free diet used in these experiments consisted of the following substances: wheat starch, 3,300 Gm.; casein (vitamin-free), 900 Gm.; Crisco, 500 Gm.; U.S.P. salt mixture No. 2, 200 Gm.; agar, 100 Gm.; yeast (type 180, Fleischmann), 140 Gm.; and yeast (type 2019, Fleischmann), 60 Gm.

EXPERIMENTAL PROCEDURE

The rats were weaned at 25 days of age and divided into two groups according to sex. The animals of each of the two groups were fed the basic diet ad libitum until they were 35 days of age. At this time one-half of the cotton rats in each of these groups were fed the vitamin A-free diet. The other one-half of the animals in each of these groups continued to receive the basic diet. Thus, the animals were divided into four groups of approximately equal numbers of vitamin A-deficient males, control males, vitamin A-deficient females, and control females. It was felt that this grouping would demonstrate differential susceptibility and immunologic response dependent on sex or upon nutrition.

The control animals which were fed the basic diet ad libitum thrived, presented no consistent abnormalities, and exhibited no particular susceptibility to intercurrent infections. Each of the control rats ate approximately 10 Gm. of the basic diet daily. On the other hand, the cotton rats which were fed the vitamin A-free diet ad libitum grew less, showed grossly a diminished deposition of fat, and exhibited increased susceptibility to intercurrent infections. Each of these rats consumed approximately 6 Gm. of the vitamin A-free diet daily.

When each animal attained the age of 8 weeks, the virus of poliomyelitis was administered by one of several experimental methods. In two experiments the virus was injected into the brain; in five it was injected or instilled into certain parts of the alimentary tract; in two it was instilled into certain parts of the respiratory tract; and in the three remaining experiments it was administered through certain unusual portals. In order to prevent death resulting from vitamin A deficiency, each vitamin A-deficient rat was returned to the basic diet two weeks after it had been inoculated with the virus.

Each animal was observed morning and evening for twenty-five days after administration of the virus. Any animal remaining free of symptoms during this interval of time was subjected to a three-way inoculation (0.1 c.c. given intracerebrally, 0.5 c.c. subcutaneously in the back and 0.06 c.c. intranasally) with a 10 per cent suspension of the virus. Cotton rats remaining free of symptoms for another twenty-five days were subjected to a second three-way reinoculation with the virus. Any animal failing to show symptoms of poliomyelitis after

the first (or original) inoculation and two three-way reinoculations with the virus was considered immune.

Each cotton rat said to have contracted poliomyelitis after its first inoculation with the virus, when the latter was administered by any route other than the intracerebral, satisfied the following four requirements: (1) Flaccid paralysis developed within twenty-five days after the virus was first administered, and observations of the animal at frequent intervals showed progressive paralysis. (2) Samples of the central nervous system showed histologic changes characteristic of anterior poliomyelitis. (3) The remaining portions of the central nervous system of the paralyzed cotton rat, when made up into a 10 per cent saline suspension and injected intracerebrally into three previously untreated cotton rats, reproduced symptoms of the disease in at least one of the three animals. (4) At least one of the three passage animals showed histologic changes in its central nervous system which are characteristic of anterior poliomyelitis.

All animals which contracted poliomyelitis were permitted to live twenty-four hours after paralysis was first observed. At the end of this period the extent of paralysis was recorded and the animal killed. The relative susceptibility of the cotton rats which contracted poliomyelitis after inoculation with the virus was judged from the number of extremities paralyzed and from the length of the incubation period (defined here as the number of days between the time of inoculation with the virus and the time the rat died or was killed). Any cotton rat in which paralysis developed in two or more extremities within fifteen days of an inoculation was considered to have no unusual resistance to the antigen.

RESULTS

Part 1. Comparative Susceptibility of Vitamin A-Deficient and Control Rats Subjected to Three-Way Inoculations and to Single Intracerebral Inoculations of the Virus.—

Experiment 1: In order to test the relative susceptibility of these experimental animals to three-way inoculations, each cotton rat was subjected to a three-way inoculation (0.1 c.c. intracerebral, 0.06 c.c. intranasal, and 0.5 c.c. subcutaneous in the back) with a 10 per cent suspension of the virus. Each of the animals in this group contracted the disease. Table I summarizes the results of this experiment.

TABLE I

ANIMALS	AVERAGE INCUBATION PERIOD (DAYS) †	EXTENT OF OBSERVABLE PARALYSIS (EXTREMITIES)
A-deficient rats* (34)	4.06 (2-8)	3.71 (2-4)
Control rats (32)	4.59 (2-8)	3.63 (2-4)
Males (34)	3.97 (2-7)	3.65 (2-4)
Females (32)	4.69 (2-8)	3.69 (2-4)
A-deficient males (18)	3.72 (2-7)	3.67 (2-4)
Control males (16)	4.25 (2-6)	3.63 (2-4)
A-deficient females (16)	4.44 (2-8)	3.75 (2-4)
Control females (16)	4.94 (2-8)	3.63 (2-4)

*Numbers in parentheses indicate number of animals.

†Defined here as the number of days between the time of inoculation with the virus and the time the rat died or was sacrificed.

Experiment 2: In order to test the relative susceptibility of these animals to intracerebral inoculation, each cotton rat was subjected to a single intracerebral inoculation with a 0.05 c.c. of a 1 per cent suspension of the virus. Every animal in this group contracted the disease. Table II summarizes the results of the experiment.

TABLE II

ANIMALS	AVERAGE INCUBATION PERIOD (DAYS)†	EXTENT OF OBSERVABLE PARALYSIS (EXTREMITIES)
A-deficient rats* (40)	5.00 (2.9)	3.10 (2.4)
Control rats (40)	4.18 (2.9)	3.15 (2.4)
Males (40)	4.65 (2.8)	3.20 (2.4)
Females (40)	4.53 (2.9)	3.05 (2.4)
A-deficient males (20)	5.00 (2.8)	3.20 (2.4)
Control males (20)	4.25 (2.8)	3.20 (2.4)
A-deficient females (20)	5.00 (2.9)	3.00 (2.4)
Control females (20)	4.10 (2.9)	3.10 (2.4)

*Numbers in parentheses indicate number of animals.

†Defined here as the number of days between the time of inoculation with the virus and the time the rat died or was sacrificed.

Part 2: Comparative Susceptibility of Vitamin A-Deficient and Control Rats Subjected to Inoculations or Instillations of the Virus Into Different Parts of the Alimentary Tract.—

Experiment 3: In order to test the relative susceptibility of these animals to food contaminated with the virus, each cotton rat devoured one brain stem and spinal cord which had been freshly removed from a cotton rat paralyzed with anterior poliomyelitis. To maintain the state of avitaminosis-A, brain stems and spinal cords fed to the vitamin A-deficient animals were in all cases removed from vitamin A-deficient cotton rats. Table III summarizes the results of this experiment.

TABLE III

ANIMALS	PARALYZED IN TWO OR MORE EXTREMITIES WITHIN USUAL INCUBATION PERIOD			RESISTANT TO TWO THREE-WAY REINOCULATIONS
	AFTER EXPERIMENTAL FEEDING	AFTER FIRST REINOCULATION	AFTER SECOND REINOCULATION	
A-deficient males (7)*	0	7	0	0
Control males (6)	0	6	0	0
A-deficient females (7)	0	7	0	0
Control females (6)	0	6	0	0

*Numbers in parentheses indicate number of animals.

Experiment 4: To test the relative susceptibility of cotton rats to virus administered through the upper pharynx, each rat received a single submucosal injection of 0.5 c.c. of a 10 per cent suspension of the virus into each of the two regions which in certain animals other than cotton rats house the palatine tonsils. Table IV summarizes the results of this experiment.

Experiment 5: This experiment was performed to test whether or not vitamin A deficiency might influence passage of viable virus through the upper gastrointestinal tract. Each cotton rat was subjected on each of three successive

TABLE IV

ANIMALS	PARALYZED IN TWO OR MORE EXTREMITIES WITHIN USUAL INCUBATION PERIOD			RESISTANT TO TWO THREE-WAY REINOCULA- TIONS
	AFTER EXPERIMENTAL INOCULATION	AFTER FIRST REINOCULA- TION	AFTER SECOND REINOCULA- TION	
A-deficient males (7)*	3	0	0	4
Control males (6)	0	0	0	6
A-deficient females (6)	2	0	0	4
Control females (7)	0	0	0	7

*Numbers in parentheses indicate number of animals.

days to a single intragastric instillation of 1.0 c.c. of a 10 per cent suspension of the virus administered by means of a stomach tube. Table V summarizes the results of this experiment.

TABLE V

ANIMALS	PARALYZED IN TWO OR MORE EXTREMITIES WITHIN USUAL INCUBATION PERIOD			RESISTANT TO TWO THREE-WAY REINOCULA- TIONS
	AFTER EXPERIMENTAL INSTILLATIONS	AFTER FIRST REINOCULA- TION	AFTER SECOND REINOCULA- TION	
A-deficient males (6)*	0	4	0	2
Control males (7)	0	7	0	0
A-deficient females (6)	0	3	0	3
Control females (7)	0	7	0	0

*Numbers in parentheses indicate number of animals.

Experiment 6: This experiment was performed to determine whether or not vitamin A deficiency might influence passage of viable virus through the lower gastrointestinal tract. Each cotton rat was subjected on each of three successive days to a single intracolonic instillation of 1.0 c.c. of a 10 per cent suspension of the virus administered by means of a rectal tube. Table VI summarizes the results of this experiment.

TABLE VI

ANIMALS	PARALYZED IN TWO OR MORE EXTREMITIES WITHIN USUAL INCUBATION PERIOD			RESISTANT TO TWO THREE-WAY INOCULATIONS
	AFTER EXPERIMENTAL INSTILLATIONS	AFTER FIRST REINOCULA- TION	AFTER SECOND REINOCULA- TION	
A-deficient males * (7)	2	0	0	5
Control males (6)	0	4	0	2
A-deficient females (7)	0	2	0	5
Control females (7)	0	5	0	2

*Numbers in parentheses indicate number of animals.

Experiment 7: In order to test the relative susceptibility of these animals to intraperitoneal inoculations, each cotton rat was subjected on each of three successive days to a single intraperitoneal inoculation with 1.0 c.c. of a 10 per cent suspension of the virus. Table VII summarizes the results of this experiment.

TABLE VII

ANIMALS	PARALYZED IN TWO OR MORE EXTREMITIES WITHIN USUAL INCUBATION PERIOD			RESISTANT TO TWO THREE-WAY INOCULATIONS
	AFTER EXPERIMENTAL INOCULATIONS	AFTER FIRST REINOCULA- TION	AFTER SECOND REINOCULA- TION	
A-deficient males* (7)	3	0	0	4
Control males (6)	0	0	0	6
A-deficient females (7)	1	0	0	6
Control females (7)	0	0	0	7

*Numbers in parentheses indicate number of animals.

Part 3. Comparative Susceptibility to Vitamin A-Deficient and Control Rats Subjected to Instillations of the Virus Into Different Parts of the Respiratory Tract.—

Experiment 8: To test whether or not vitamin A deficiency might alter susceptibility to virus entering through the upper respiratory tract, each cotton rat was subjected during the morning and again during the evening on each of three successive days to an intranasal instillation with the virus of poliomyelitis. On each of these occasions, 0.05 c.c. of a 10 per cent suspension of the virus was dropped into each nostril. Table VIII summarizes the results of this experiment.

TABLE VIII

ANIMALS	PARALYZED IN TWO OR MORE EXTREMITIES WITHIN USUAL INCUBATION PERIOD			RESISTANT TO TWO THREE-WAY INOCULATIONS
	AFTER EXPERIMENTAL INSTILLATIONS	AFTER FIRST REINOCULA- TION	AFTER SECOND REINOCULA- TION	
A-deficient males* (6)	0	6	0	0
Control males (7)	0	7	0	0
A-deficient females (7)	1	6	0	0
Control females (6)	0	6	0	0

*Numbers in parentheses indicate number of animals.

Experiment 9: To test the relative permeability of the pulmonary epithelium to the virus of poliomyelitis, each cotton rat was subjected to a single intra-bronchial instillation of 0.1 c.c. of a 10 per cent suspension of virus by means of a tracheal catheter. Table IX summarizes the results of this experiment.

TABLE IX

ANIMALS	PARALYZED IN TWO OR MORE EXTREMITIES WITHIN USUAL INCUBATION PERIOD			RESISTANT TO TWO THREE-WAY INOCULATIONS
	AFTER EXPERIMENTAL INSTILLATIONS	AFTER FIRST REINOCULA- TION	AFTER SECOND REINOCULA- TION	
A-deficient males* (7)	0	7	0	0
Control males (6)	0	6	0	0
A-deficient females (7)	0	7	0	0
Control females (7)	0	7	0	0

*Numbers in parentheses indicate number of animals.

TABLE X

ANIMALS	PARALYZED IN TWO OR MORE EXTREMITIES WITHIN USUAL INCUBATION PERIOD			RESISTANT TO TWO THREE-WAY INOCULATIONS
	AFTER EXPERIMENTAL INOCULATIONS	AFTER FIRST REINOCULA- TION	AFTER SECOND REINOCULA- TION	
A-deficient males* (6)	1	0	0	5
Control males (7)	0	0	0	7
A-deficient females (7)	0	0	0	7
Control females (7)	0	1	0	6

*Numbers in parentheses indicate number of animals.

Part 4. Comparative Susceptibility of Vitamin A-Deficient and Control Rats Subjected to the Virus Administered by Unusual Methods.—

Experiment 10: This experiment was performed to determine whether or not vitamin A deficiency might influence susceptibility when the virus was introduced beneath the skin. Each cotton rat was subjected on each of three successive days to a single subcutaneous inoculation with a 1.0 c.c. of a 10 per cent suspension of the virus. Table X summarizes the results of this experiment.

Experiment 11: This experiment was performed to determine whether or not vitamin A deficiency might influence susceptibility when the virus was introduced into the blood stream by means of cardiac puncture. Each cotton rat was subjected to a single intracardiac inoculation of 0.5 c.c. of a 10 per cent suspension of the virus. Table XI summarizes the results of this experiment.

TABLE XI

ANIMALS	PARALYZED IN TWO OR MORE EXTREMITIES WITHIN USUAL INCUBATION PERIOD			RESISTANT TO TWO THREE-WAY INOCULATIONS
	AFTER EXPERIMENTAL INOCULATIONS	AFTER FIRST REINOCULA- TION	AFTER SECOND REINOCULA- TION	
A-deficient males* (6)	2	2	0	2
Control males (7)	0	0	0	7
A-deficient females (6)	0	0	0	6
Control females (6)	0	1	0	5

*Numbers in parentheses indicate number of animals.

Experiment 12: This experiment was performed to determine whether or not vitamin A deficiency might influence susceptibility following contact with a diseased animal. Each cotton rat was permitted to live in the same cage with

TABLE XII

ANIMALS	PARALYZED IN TWO OR MORE EXTREMITIES WITHIN USUAL INCUBATION PERIOD			RESISTANT TO TWO THREE-WAY INOCULATIONS
	AFTER EXPERIMENTAL CONTACT	AFTER FIRST REINOCULA- TION	AFTER SECOND REINOCULA- TION	
A-deficient males* (7)	0	7	0	0
Control males (6)	0	6	0	0
A-deficient females (6)	0	6	0	0
Control females (6)	0	6	0	0

*Numbers in parentheses indicate number of animals.

another cotton rat which had been subjected to a three-way inoculation with the virus. The experimental cotton rat remained in intimate contact with the inoculated animal until the latter became completely paralyzed. Table XII summarizes the results of this experiment.

COMMENT

It is conceivable that as a consequence of feeding vitamin A-deficient diets an altered susceptibility to paralytic anterior poliomyelitis might result because: (1) certain epithelia, which ordinarily would be impermeable to the virus, may be altered in such a manner that they would permit its passage; and/or (2) the "internal resistance" of the host (neutralizing substance, circulating virucidal substances, cellular resistance) may be less effective.

The results obtained in this study from experiments in which the virus was administered by intracerebral injections (Experiments 1 and 2), by feeding an infected brain stem and spinal cord (Experiment 3), by intrapulmonary instillations (Experiment 9) and by contact with an infected animal (Experiment 12), offered no evidence to indicate that susceptibility to the virus of poliomyelitis is related to vitamin A-deficient diets, to partial inanition or to sex. Whereas none of the animals in Experiments 3, 9, and 12 acquired the disease following their first exposure to the virus, it is interesting to note that all of these animals contracted the disease following three-way inoculations which were administered twenty-five days after their first exposure to the virus. Since none of these animals exhibited any unusual resistance to three-way inoculations, these results would indicate that during their first exposure little or no active virus entered the body through the epithelial membranes of the alimentary and respiratory tracts or the skin.

In contrast to these findings, the results of experiments in which the virus was administered by intratonsillar injections (Experiment 4); by intracolonic instillations (Experiment 6); by intraperitoneal injections (Experiment 7); by intranasal instillations (Experiment 8); by subcutaneous injections (Experiment 10) and by intracardiac injections (Experiment 11); indicate that cotton rats fed vitamin A-deficient diets are more susceptible to the virus of poliomyelitis than are rats which have been fed an adequate diet.

Whereas none of the animals which were given the virus by stomach tube (Experiment 5), and only two of the animals administered the virus by intracolonic instillation (Experiment 6), acquired the disease, a considerable number of the vitamin A-deficient rats in both of these experiments exhibited complete resistance to three-way inoculations which were administered twenty-five days after the rat was first exposed to the virus. These results seem to indicate that during their first exposure enough of the virus leaked through the epithelium of the alimentary tract to produce an acquired immunity to the disease.

The experiments reported in this communication do not indicate what effect partial inanition (each of the vitamin A-deficient rats consumed only about 60 per cent as much food as did the controls) might have on the susceptibility of cotton rats to the virus of poliomyelitis. In this regard, findings of previous

TABLE X

ANIMALS	PARALYZED IN TWO OR MORE EXTREMITIES WITHIN USUAL INCUBATION PERIOD			RESISTANT TO TWO THREE-WAY INOCULATIONS
	AFTER EXPERIMENTAL INOCULATIONS	AFTER FIRST REINOCULA- TION	AFTER SECOND REINOCULA- TION	
A-deficient males* (6)	1	0	0	5
Control males (7)	0	0	0	7
A-deficient females (7)	0	0	0	7
Control females (7)	0	1	0	6

*Numbers in parentheses indicate number of animals.

Part 4. Comparative Susceptibility of Vitamin A-Deficient and Control Rats Subjected to the Virus Administered by Unusual Methods.—

Experiment 10: This experiment was performed to determine whether or not vitamin A deficiency might influence susceptibility when the virus was introduced beneath the skin. Each cotton rat was subjected on each of three successive days to a single subcutaneous inoculation with a 1.0 c.c. of a 10 per cent suspension of the virus. Table X summarizes the results of this experiment.

Experiment 11: This experiment was performed to determine whether or not vitamin A deficiency might influence susceptibility when the virus was introduced into the blood stream by means of cardiac puncture. Each cotton rat was subjected to a single intracardiac inoculation of 0.5 c.c. of a 10 per cent suspension of the virus. Table XI summarizes the results of this experiment.

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	AFTER EXPERIMENTAL INOCULATIONS	AFTER FIRST REINOCULA- TION	AFTER SECOND REINOCULA- TION	
A-deficient males* (6)	2	2	0	2
Control males (7)	0	0	0	7
A-deficient females (6)	0	0	0	6
Control females (6)	0	1	0	5

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Experiment 12: This experiment was performed to determine whether or not vitamin A deficiency might influence susceptibility following contact with a diseased animal. Each cotton rat was permitted to live in the same cage with

TABLE XII

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	AFTER EXPERIMENTAL CONTACT	AFTER FIRST REINOCULA- TION	AFTER SECOND REINOCULA- TION	
A-deficient males* (7)	0	7	0	0
Control males (6)	0	6	0	0
A-deficient females (6)	0	6	0	0
Control females (6)	0	6	0	0

*Numbers in parentheses indicate number of animals.

another cotton rat which had been subjected to a three-way inoculation with the virus. The experimental cotton rat remained in intimate contact with the inoculated animal until the latter became completely paralyzed. Table XII summarizes the results of this experiment.

COMMENT

It is conceivable that as a consequence of feeding vitamin A-deficient diets an altered susceptibility to paralytic anterior poliomyelitis might result because: (1) certain epithelia, which ordinarily would be impermeable to the virus, may be altered in such a manner that they would permit its passage; and/or (2) the "internal resistance" of the host (neutralizing substance, circulating virucidal substances, cellular resistance) may be less effective.

The results obtained in this study from experiments in which the virus was administered by intracerebral injections (Experiments 1 and 2), by feeding an infected brain stem and spinal cord (Experiment 3), by intrapulmonary instillations (Experiment 9) and by contact with an infected animal (Experiment 12), offered no evidence to indicate that susceptibility to the virus of poliomyelitis is related to vitamin A-deficient diets, to partial inanition or to sex. Whereas none of the animals in Experiments 3, 9, and 12 acquired the disease following their first exposure to the virus, it is interesting to note that all of these animals contracted the disease following three-way inoculations which were administered twenty-five days after their first exposure to the virus. Since none of these animals exhibited any unusual resistance to three-way inoculations, these results would indicate that during their first exposure little or no active virus entered the body through the epithelial membranes of the alimentary and respiratory tracts or the skin.

In contrast to these findings, the results of experiments in which the virus was administered by intratonsillar injections (Experiment 4); by intracolonic instillations (Experiment 6); by intraperitoneal injections (Experiment 7); by intranasal instillations (Experiment 8); by subcutaneous injections (Experiment 10) and by intracardiac injections (Experiment 11); indicate that cotton rats fed vitamin A-deficient diets are more susceptible to the virus of poliomyelitis than are rats which have been fed an adequate diet.

Whereas none of the animals which were given the virus by stomach tube (Experiment 5), and only two of the animals administered the virus by intracolonic instillation (Experiment 6), acquired the disease, a considerable number of the vitamin A-deficient rats in both of these experiments exhibited complete resistance to three-way inoculations which were administered twenty-five days after the rat was first exposed to the virus. These results seem to indicate that during their first exposure enough of the virus leaked through the epithelium of the alimentary tract to produce an acquired immunity to the disease.

The experiments reported in this communication do not indicate what effect partial inanition (each of the vitamin A-deficient rats consumed only about 60 per cent as much food as did the controls) might have on the susceptibility of cotton rats to the virus of poliomyelitis. In this regard, findings of previous

studies on vitamin B and D deficiencies³ (during these experiments the deficient animals also suffered from partial inanition) are of importance. In this series no evidence was found that partial inanition, per se or in conjunction with vitamins B and D deficiencies, significantly influenced the susceptibility of cotton rats to the virus of poliomyelitis. If partial inanition plays any part in lowering the resistance of vitamin A-deficient cotton rats to the virus of poliomyelitis, it must be of minor importance.

It is commonly recognized that the male is more susceptible to the paralytic form of anterior poliomyelitis than is the female.⁵ It is interesting to note that in the present investigation, of the fifteen vitamin A-deficient rats which contracted the paralytic form of the disease after the virus was administered by methods other than by intracerebral injection, only two were females. However, it would appear that the increased susceptibility evidenced by the males is not due primarily to sex because: (1) previous studies³ showed no difference in susceptibility which could be attributed to sex, and (2) in the present investigation, the differences in susceptibility which could be related to sex were apparent only among the vitamin A-deficient animals.

Considerable caution should be exercised in applying to the human being our findings that vitamin A-deficient diet increases the susceptibility of cotton rats to the virus of poliomyelitis. Whereas the pathologic consequences of avitaminosis-A are similar in both species,⁴ it is questionable whether the human being ever suffers from this type of malnutrition to the degree experienced by our animals.

SUMMARY AND CONCLUSIONS

This communication records the results of twelve experiments which were designed to test the effects of vitamin A-deficient diets, of partial inanition, and of sex on the susceptibility and on certain immunologic responses of cotton rats to the virus of poliomyelitis.

Suspensions of the Armstrong-Lansing strain of the virus of poliomyelitis were injected or instilled in varying quantities into the cerebrum, stomach, colon, peritoneal cavity, external nares, and blood stream, beneath the skin of the back and beneath the pharyngeal mucosa. In addition, the animals of one experimental group were allowed to remain in intimate contact with cotton rats succumbing to the effects of intracerebral inoculations with the virus. Finally, each cotton rat of still another experimental group was fed the brain stem and spinal cord freshly removed from a cotton rat paralyzed with poliomyelitis.

Each of the cotton rats which failed to develop paralysis after an experimental inoculation with the virus was subjected to three-way reinoculations with the virus at intervals of twenty-five days.

The results of these experiments yield no evidence to indicate that vitamin A-deficient diets affect the susceptibility or the resistance of cotton rats to the virus of poliomyelitis when the latter is administered by injections into the cerebrum, by instillations into the bronchi, by feeding an infected brain stem and spinal cord, or by contact with an infected cotton rat.

Evidence was presented to indicate that cotton rats fed vitamin A-deficient diets are more susceptible to the virus of poliomyelitis than are controls when the virus is administered by intratonsillar injections, by intracolonic instillations, by intraperitoneal injections, by intranasal instillations, by subcutaneous injections and by intracardiac injections.

Some evidence was presented to indicate that, in cotton rats fed vitamin A-deficient diets, the mucosa of certain parts of the alimentary tract may become more permeable to the virus of poliomyelitis than is the case among the controls.

It would appear that sex and partial inanition, suffered by all vitamin A-deficient rats, played no primary part in the results obtained in this study.

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THE USE OF SULFAMERAZINE IN INFANTS AND CHILDREN

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SULFAMERAZINE* (2-sulfanilamido-4-methylpyrimidine), the monomethyl derivative of sulfadiazine,¹ is in fairly wide clinical use at the present time, and certain advantages have been claimed for it over the other commonly employed sulfonamide drugs, particularly sulfadiazine: (1) Sulfamerazine is more quickly and completely absorbed from the gastrointestinal tract^{2, 3} and therefore may be satisfactorily administered orally in many instances in which parenteral administration would be more desirable if certain of the other sulfonamide drugs were used. (2) Sulfamerazine is excreted much more slowly by the kidney than either sulfadiazine or sulfathiazole^{2, 4} and for this reason may be administered at less frequent intervals and in smaller amounts with the attainment of comparable levels in the blood. (3) The therapeutic value of sulfamerazine has proved to be equal to that of sulfadiazine and sulfathiazole both in the treatment of infections in human beings and in experimental infections in animals.⁵⁻⁸ (4) The toxic effects of sulfamerazine are certainly no greater and possibly somewhat less than those of sulfadiazine and sulfathiazole.^{2, 5, 6, 9}

Since the methods of administration of the various sulfonamide drugs to adults cannot be applied satisfactorily to the treatment of infants and children and since the toxic effects in infants and children and in adults may vary considerably, we have undertaken a study of the use of sulfamerazine in patients in the pediatric age group for the primary purpose of establishing a rational dosage scheme for both oral and parenteral administration of the drug. As the work continued, it seemed desirable to include observations on the distribution of sulfamerazine in the various body fluids, on the toxic effects of the drug, and in a limited way on its therapeutic usefulness. The study embraced the period from December, 1943, through June, 1944, during which time 135 unselected hospitalized infants and children with various types of infections were treated with sulfamerazine.

THE ABSORPTION OF SULFAMERAZINE FROM THE GASTROINTESTINAL TRACT

Single oral doses of sulfamerazine of 0.1 Gm. per kilogram body weight were given to a number of children,[†] and the level of free sulfamerazine[‡] in the blood was determined at intervals during the succeeding twenty-four hours. The results are shown in Fig. 1 in which the subjects are divided into two groups, those two years of age or older and those in the first or second year of life. It is evident from the average values indicated at the top of each portion of the chart

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*A portion of the sulfamerazine used in this study was provided through the courtesy of the Medical Research Division of Sharp & Dohme, Inc.

[†]Patients with known renal or enteric disease were carefully excluded from this portion of the study.

[‡]The analyses for sulfamerazine in the blood and other body fluids were made by the method of Bratton and Marshall,¹⁰ adapted for a sample of 0.1 c.c. Unless otherwise indicated, all values for sulfamerazine in this paper are for the free form of the drug.

that the absorption of the drug is somewhat better in the older age group. The average blood concentration is seen to increase until the eighth hour following administration and then to fall very gradually, so that there is still an appreciable concentration at the end of twenty-four hours. It may be concluded that sulfamerazine is absorbed rapidly from the gastrointestinal tract and is excreted rather slowly. There is, however, considerable individual variation in the rate of both absorption and excretion.

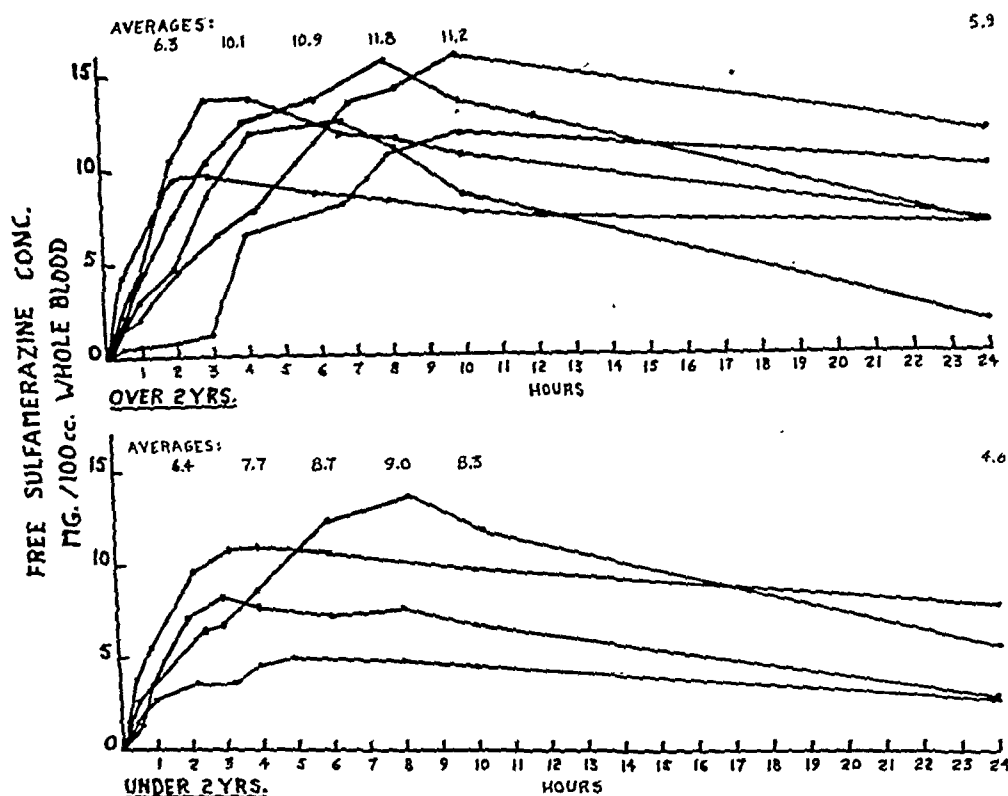


FIG. 1.—Blood concentrations of free sulfamerazine following single oral doses of 0.1 Gm. of sulfamerazine per kilogram body weight to children 2 years of age and older and to infants.

Since sulfamerazine is so readily absorbed from the gastrointestinal tract, an attempt was made to attain very high blood concentrations of the drug in young infants through oral administration alone. Fig. 2 illustrates the results of giving a single oral dose of 0.4 Gm. per kilogram of body weight. The average blood values are seen to be somewhat greater than those in the infants who received 0.1 Gm. per kilogram of body weight, but the differences are not marked. The larger dose resulted in about the same blood level at two hours as did the smaller; in one case the level finally reached 21.4 mg. per cent, but only after twenty-four hours. It is apparent, as in the case of the other sulfonamide drugs, that infants are not able to absorb rapidly from the gastrointestinal tract very large amounts of sulfamerazine. In time, high concentrations could

doubtless be achieved in this manner, but usually in critically ill patients it is desirable to obtain the high blood levels quickly.

The matter of proper maintenance dosage of the drug for sick infants and children was considered, and the following dosage scheme was decided upon: an initial dose of 0.1 Gm. of sulfamerazine per kilogram body weight to be followed by 0.05 Gm. per kilogram body weight at eight-hour intervals. The total daily dosage then amounts to 0.15 Gm. per kilogram body weight or three-

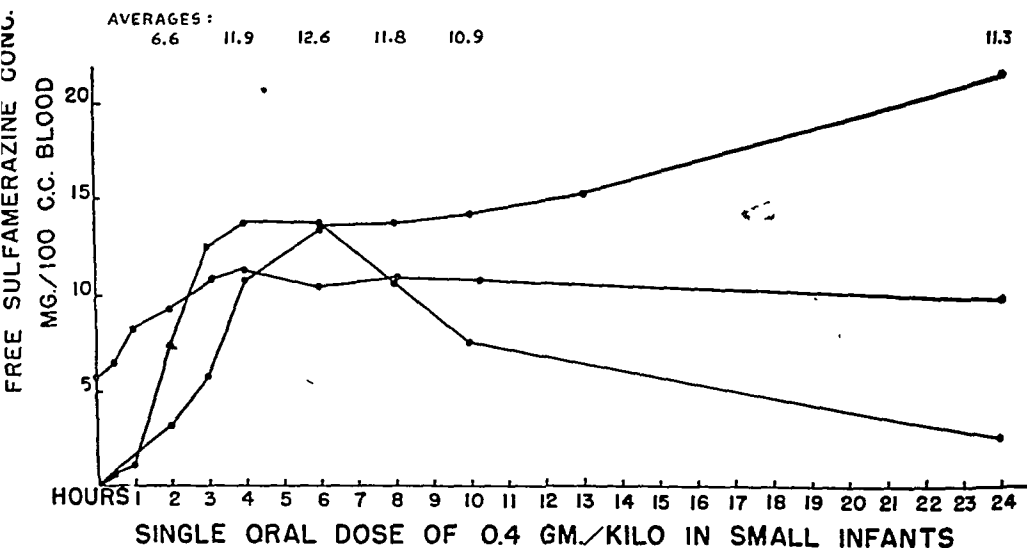


Fig. 2.—Blood concentrations of free sulfamerazine following single oral doses of 0.4 Gm. of sulfamerazine per kilogram body weight to infants in the first year of life.

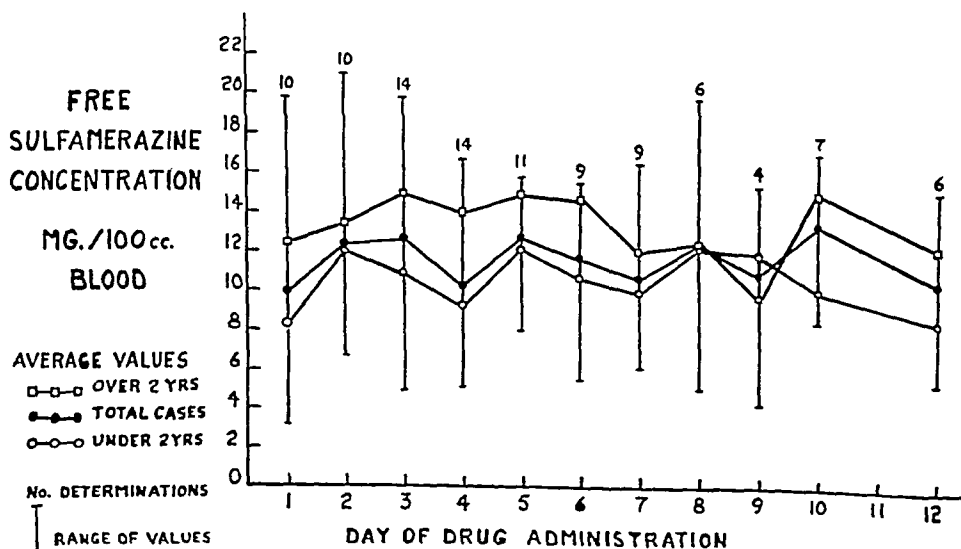


Fig. 3.—Blood concentrations of free sulfamerazine produced by the repeated oral administration of 0.05 Gm. of sulfamerazine per kilogram body weight every 8 hours to children of various ages, following an initial dose of 0.1 Gm. per kilogram body weight.

fourths of the dosage usually employed with the other sulfonamide drugs. In treating older children, a daily dose of 5.0 Gm. is not exceeded regardless of the patient's weight. It will be seen (Fig. 3) that in older children the average blood levels varied from 10 to 15 mg. per cent and in infants from 8 to 12 mg. per cent. Such levels are adequate in the treatment of patients with infections which are not unusually severe.

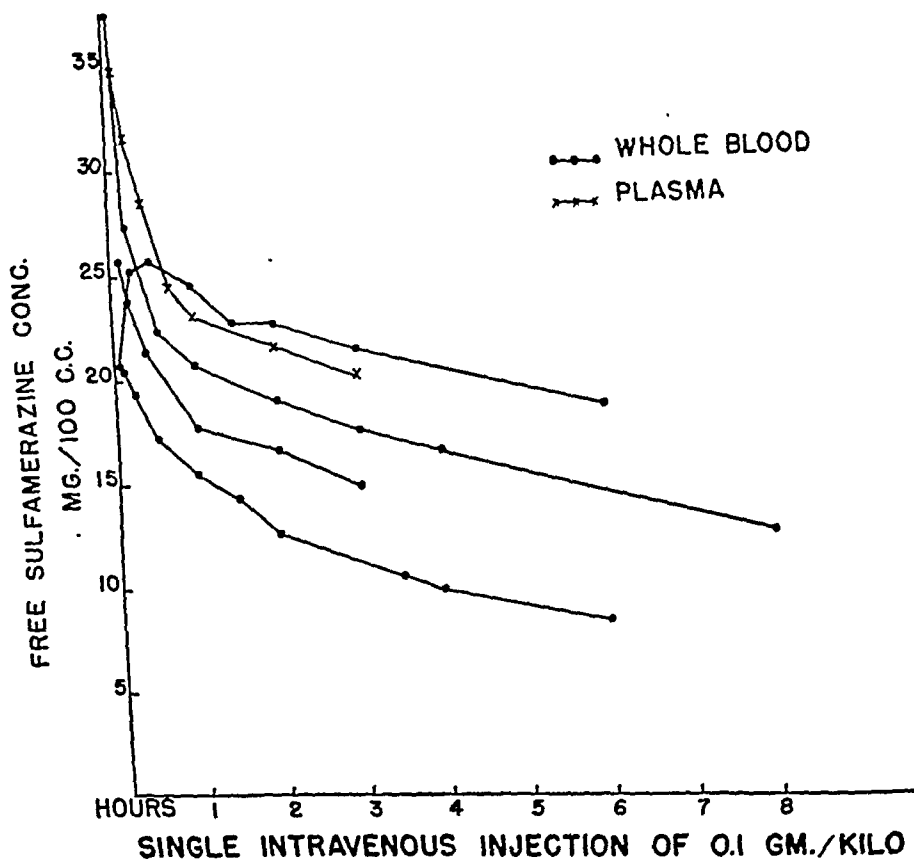


Fig. 4.—Blood concentrations of free sulfamerazine following a single intravenous injection of 0.1 Gm. of sodium sulfamerazine per kilogram body weight, made up as a 5 per cent solution in distilled water.

PARENTERAL ADMINISTRATION OF SODIUM SULFAMERAZINE

Intravenous Administration.—Fig. 4 illustrates the blood levels following a single intravenous injection of 0.1 Gm. of sodium sulfamerazine per kilogram body weight. The drug was prepared as a 5 per cent solution in distilled water. The concentration, after the high initial peak, dropped rapidly during the first hour following the injection and then decreased gradually. The blood levels were not followed for longer than eight hours since the rate of excretion after this period is largely independent of the mode of administration of the drug.

Subcutaneous Administration.—A special study was made of this method of administration since it seems to be preferable when any of the sulfonamide

drugs are to be given parenterally. Adequate blood levels may be attained promptly; the technique of administration is easy and, therefore, particularly desirable when the injection must be repeated many times; the injection can also provide water and alkali at the same time that the drug is being given; the initial undesirably high blood concentration which occurs after intravenous injection is obviated. Fig. 5 illustrates the blood levels obtained with subcutaneous

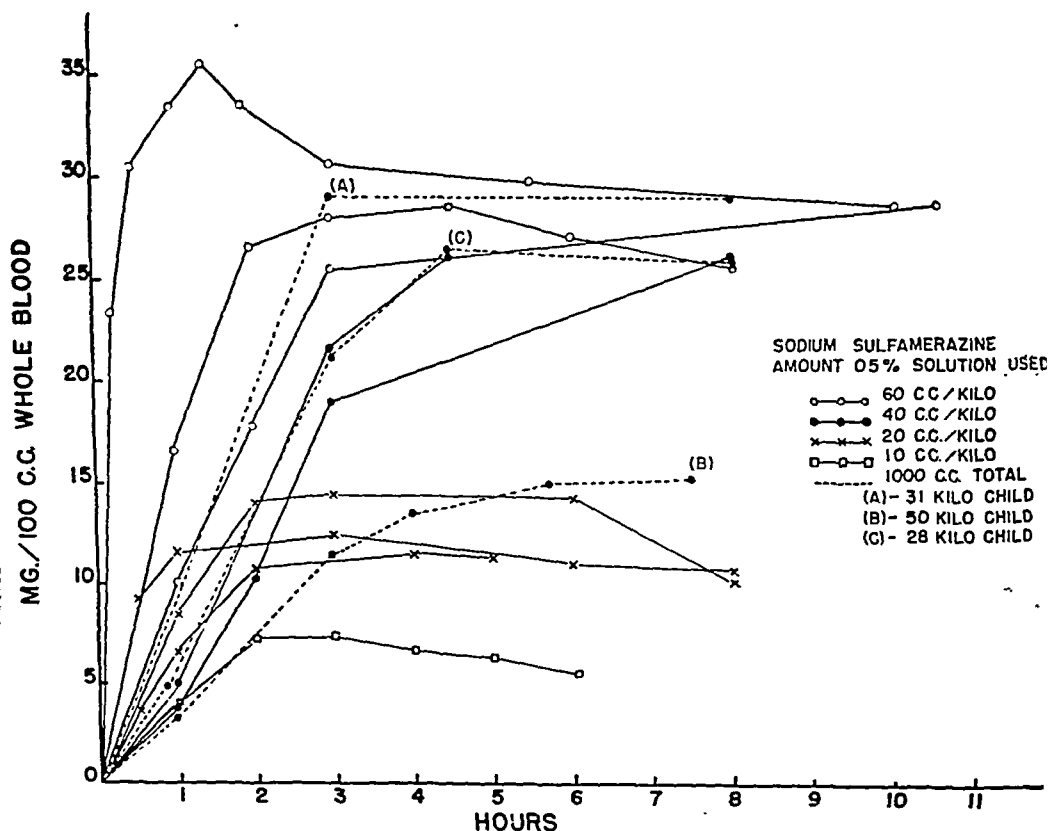


Fig. 5.—Blood concentrations of free sulfamerazine following single subcutaneous injections of varying amounts of 0.5 per cent sodium sulfamerazine in half "fortified lactate Ringer's" solution.

administration of varying amounts of 0.5 per cent sodium sulfamerazine. The drug was made up in either plain or half "fortified lactate Ringer's" solution and administered as an ordinary hypodermoclysis. No local reaction was observed even when concentrations of 1 per cent were used, and pain seemed to be no greater than that occurring with other hypodermoclyses.

As the amount of solution given is increased from 10 c.c. per kilogram body weight to 60 c.c. per kilogram (i.e., 0.05 Gm. to 0.3 Gm. of drug per kilogram), the rate of absorption is seen to be more rapid and the blood level attained in a

*Plain lactate Ringer's: A solution of $\frac{1}{40}$ molar sodium-r-lactate in slightly hypotonic Ringer's.

Half "fortified lactate Ringer's": A mixture of three parts by volume of $\frac{1}{4}$ molar sodium-r-lactate and four parts of Ringer's solution.

given period of time higher. Ten cubic centimeters of 0.5 per cent solution per kilogram does not produce an adequate blood level, whereas 20 c.c. (0.1 Gm.) per kilogram results in a level about equal to that produced by the same amount of drug given orally. The 40 c.c. and 60 c.c. per kilogram doses produce a high blood level with a rapidity which is quite adequate in patients with severe infections. The uppermost curve was obtained on a very dehydrated child; the speed of absorption here was amazing, the blood level reaching 23.4 mg. per cent within fifteen minutes.

The curves marked (A), (B), and (C) represent cases in which 1,000 c.c. of 0.5 per cent solution of sodium sulfamerazine was given to children of various weights. This amount seems adequate for most larger children, and we have not found it necessary to give single doses of more than 5.0 Gm. of drug to a child by this route regardless of body weight. In adults, the administration of 5.0 Gm. of sodium sulfamerazine subcutaneously every eight hours has resulted in blood levels of between 20 and 30 mg. per cent.¹¹

THE ADMINISTRATION OF SULFAMERAZINE TO PATIENTS WITH SEVERE INFECTIONS

On the basis of these observations we attempted to work out a rational scheme for rapidly attaining blood concentrations of 25 to 30 mg. per cent and maintaining such levels until the patient's infection is definitely subsiding. Fig. 6 illustrates the scheme in the treatment of a disease such as meningococcal meningitis; that is, one which is severe yet responds rapidly to sulfonamide therapy. For the first two days the drug is given subcutaneously, the initial dose being 60 c.c. of a 0.5 per cent solution per kilogram body weight. Subsequent doses of 20 c.c. per kilogram are given at eight-hour intervals. The blood concentration usually reaches 25 mg. per cent within two hours after the beginning of treatment and is maintained, on the average, near 30 mg. per cent for the next two days. At the end of this time the patient is often able to take oral medication, the very high blood level is no longer as essential, and thereafter sulfamerazine is administered orally in doses of 0.1 Gm. per kilogram every eight hours. The average blood level then usually drops to between 15 and 20 mg. per cent where it is maintained until the infection is well under control. Subsequent therapy consists of giving the patient 0.05 Gm. per kilogram every eight hours. In Fig. 6 are shown the values obtained in five patients, all suffering from acute purulent meningitis, the average blood concentrations being indicated by the clear line in the center of the black area.

In cases of meningitis due to the pneumococcus, hemolytic streptococcus, or the influenzal bacillus, in which high drug levels should be maintained for longer periods of time, subcutaneous sodium sulfamerazine may be continued as long as necessary. With careful following of the blood concentrations of sulfamerazine, the dosage may be adjusted to produce suitable levels. With the ease of subcutaneous administration of the drug and the absence of local irritation from the injection, we have been able to administer sodium sulfamerazine to several patients by the subcutaneous route alone for as long as three weeks without untoward effects.

It is essential, however, that daily blood determinations of the drug should be made when subcutaneous administration is being employed in such dosages. While Fig. 6 indicates that the average blood concentrations attained were satisfactory when the described schemes were used, it also illustrates that considerable variation may occur. For example, at the end of the second day, the spread exhibited by the five patients was from 20.8 mg. per cent to 40.8

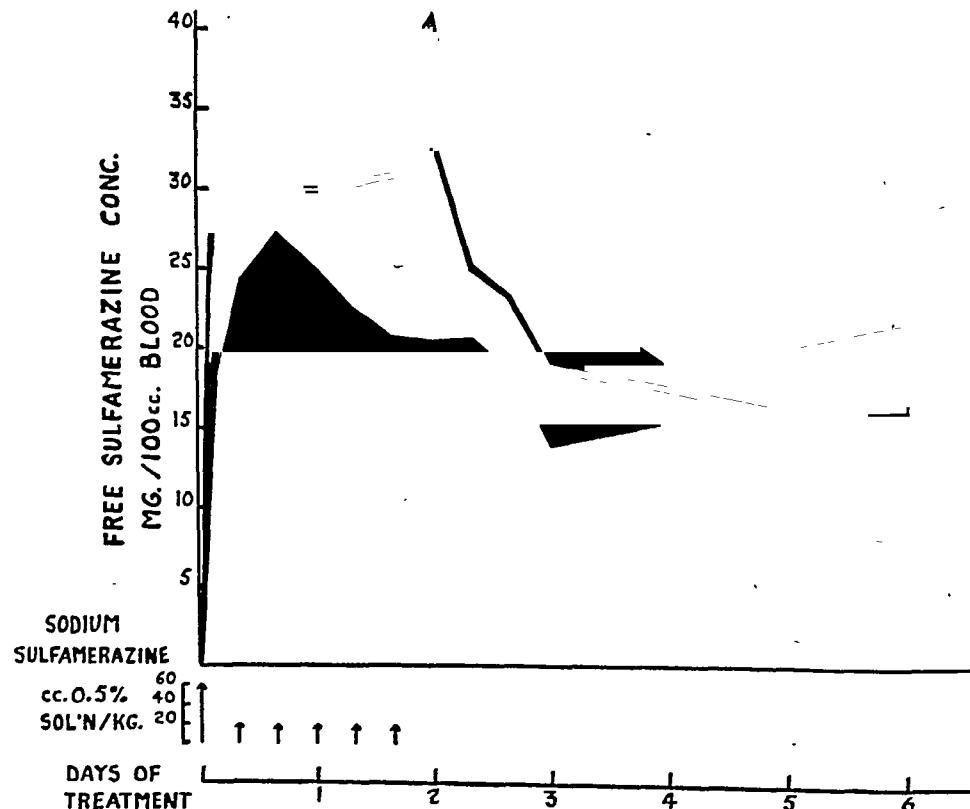


Fig. 6.—Blood concentrations of free sulfamerazine produced by the repeated subcutaneous administration of 0.5 per cent sodium sulfamerazine at eight-hour intervals, followed by oral doses of 0.1 Gm. of sulfamerazine per kilogram body weight given every eight hours.

mg. per cent despite the fact that they were given identical doses of sulfamerazine on the basis of body weight. In general, in any given patient, one can predict more closely the blood concentration when the drug is administered orally in ordinary dosages (0.15 Gm. per kilogram per day) than when higher dosages are employed. Finally, it should be remembered that parenteral administration of sulfamerazine is essential for the attainment of very high blood concentrations, particularly in small infants.

THE DISTRIBUTION OF SULFAMERAZINE IN THE VARIOUS BODY FLUIDS

It has been reported that sulfamerazine passes into the cerebrospinal fluid to the extent of about 50 per cent of the concentration in whole blood.^{3, 6} This

value is in keeping with the relatively high degree of binding of the drug by plasma proteins.^{4, 12} However, in the reported observations, no indication is given of the variation in the concentration of the drug in the blood during the several hours preceding the withdrawal of blood and spinal fluid for analysis. Although changes in the blood level are reflected in the spinal fluid, the change in spinal fluid concentration may lag considerably. This phenomenon probably accounts for the considerable variation in the ratio of spinal fluid to blood concentration which is so often noted in clinical practice and also for the fact that occasionally the concentration in the spinal fluid may actually exceed that in the blood in isolated samplings. With this in mind, we attempted to determine the ratios of the drug concentration in various body fluids to that in whole blood and plasma on occasions when it was known that the blood concentration had not changed markedly during the four-hour period prior to obtaining the blood and other body fluid specimens on which these ratios were calculated.

The data obtained are shown in Table I which includes observations on spinal fluid, pleural fluid, and ascitic fluid. The studies involving spinal fluid were all performed on patients suffering from either purulent or tuberculous meningitis, and those on pleural and ascitic fluid on a patient in the nephrotic stage of chronic glomerulonephritis who had a plasma albumin concentration of only 1.1 Gm. per cent. Metycaine* was used as a local anesthetic prior to withdrawal of all fluids for sulfamerazine analysis.

TABLE I. DISTRIBUTION OF SULFAMERAZINE IN VARIOUS BODY FLUIDS

CASE	DATE	DAY OF DRUG THERAPY	VARIATION IN BLOOD LEVEL DURING PRECEDING 4 HOURS (%)	WHOLE BLOOD (MG. %)	PLASMA (MG. %)	SPINAL FLUID (MG. %)	RATIOS	
							SPINAL FLUID WHOLE BLOOD (%)	SPINAL FLUID PLASMA (%)
E. W.	3/ 9/44	3	10.6	34.7	40.3	28.9	83.3	71.7
J. B.	3/18/44	3	7.1	34.0	35.9	20.8	61.2	58.0
J. H.	5/ 1/44	3	8.3	27.4	32.3	20.3	74.1	62.8
J. M.	5/ 7/44	7	12.9	38.4	43.6	25.5	66.4	58.2
D. K.	5/11/44	7	14.5	41.7	44.2	32.1	76.9	72.6
D. K.	5/16/44	12	3.5	13.8	18.6	8.7	63.0	46.7
B. E.	5/11/44	13	1.1	17.0	21.0	8.7	51.3	41.4
Average							68.0	58.9

CASE	DATE	DAY OF DRUG THERAPY	VARIATION IN BLOOD LEVEL DURING PRECEDING 4 HOURS (%)	WHOLE BLOOD (MG. %)	PLASMA (MG. %)	PLEURAL FLUID (MG. %)	PLEURAL FLUID WHOLE BLOOD (%)	PLEURAL FLUID PLASMA (%)
D. D.	4/11/44	2	1.1	11.1	11.0	10.1	91.0	92.0
D. D.	4/12/44	3	2.0	10.8	11.4	11.4	105.0	100.0

CASE	DATE	DAY OF DRUG THERAPY	VARIATION IN BLOOD LEVEL DURING PRECEDING 4 HOURS (%)	WHOLE BLOOD (MG. %)	PLASMA (MG. %)	ASCITIC FLUID (MG. %)	ASCITIC FLUID WHOLE BLOOD (%)	ASCITIC FLUID PLASMA (%)
D. D.	4/11/44	2	1.1	11.1	11.0	10.6	95.5	96.5
D. D.	4/12/44	3	2.0	10.8	11.4	10.9	101.0	95.6

*Gamma-(2-methylpiperidino) propylbenzoate hydrochloride, Eli Lilly and Company.

The ratios of the drug concentration in spinal fluid to that in whole blood and in plasma averaged 68 per cent and 59 per cent, respectively, and do not differ greatly from those for sulfadiazine and sulfapyrazine but are distinctly higher than those for sulfathiazole.

The data on the concentration of sulfamerazine in ascitic and pleural fluid indicate that in the one patient we observed, the drug distributed itself approximately equally between those fluids and the blood plasma, a finding in agreement with the earlier observations of Hageman and his coworkers.⁶ Murphy and his coworkers,³ however, found a much lower rate to exist between pleural and ascitic fluid and blood serum. It is possible that the very low plasma albumin in the patient which we studied may have affected somewhat the degree of binding of the drug in the plasma and, therefore, may have influenced its distribution between the plasma and the fluids mentioned.

THE EFFECTIVENESS OF SULFAMERAZINE IN VARIOUS CLINICAL INFECTIONS

A total of 135 unselected infants and children with various infections were treated with sulfamerazine during the course of this study. The drug was administered in accordance with the plans we have outlined. High drug dosages were employed in those patients suffering from meningitis, peritonitis, and severe respiratory infections and the lower dosages in those with the less severe infections. In treating these patients an attempt was made to compare the course of the illness with that in patients treated in the past with other sulfonamide drugs.

Acute Meningitis.—Seventeen patients with acute meningococcic meningitis were treated with sulfamerazine; all of these recovered. The response to treatment was prompt in each case and quite satisfactory from the standpoint of both clinical and laboratory findings.

Sulfamerazine was used in one case of pneumococcal meningitis and mastoiditis and one case of influenzal (type B) meningitis with satisfactory recoveries in both. One case of hemolytic streptococcal meningitis was treated with sulfamerazine; penicillin was also used, however, so the effectiveness of the sulfamerazine cannot be evaluated.

Sulfamerazine was administered in high dosage in one case of tuberculous meningitis. There was no observable effect on the course of the infection.

Acute Peritonitis.—Four cases were treated. Two of these were due to the colon bacillus. In one, the infection was primary; in the other a generalized peritonitis secondary to an acute appendicitis was present. There was recovery in both. One patient whose case was of pneumococcal origin died within twelve hours of the onset of therapy. The fourth patient, who also died, was a young infant who suffered from cirrhosis of the liver, the organism responsible for the peritonitis being the *Staphylococcus aureus*.

Infections of the Upper Respiratory Tract.—Six cases of acute streptococcal tonsillitis were treated, all of which exhibited prompt alleviation of symptoms. Two cases of acute laryngitis, due to the streptococcus, responded well to sulfamerazine, although in one of these a tracheotomy was necessary to relieve dyspnea. The response to treatment was quite striking in a one-year-old infant who had developed acute thyroiditis secondary to acute tonsillitis and laryngitis.

Infections of the Lower Respiratory Tract.—Ten cases of typical lobar pneumonia were treated with sulfamerazine, and prompt improvement occurred in each case. One case of pneumococcal empyema with bacteremia improved after the institution of surgical drainage and the use of sulfamerazine. Six patients with bronchopneumonia, all of them small infants, improved promptly with sulfamerazine therapy. Six cases of severe bronchitis did well under treatment with the drug.

Miscellaneous Infections.—Those cases in which an evaluation of the effectiveness of sulfamerazine seemed possible are as follows: two cases of erysipelas, one of acute colon bacillus pyelitis, one of cellulitis of the thigh with accompanying femoral adenitis, and two cases of exfoliative dermatitis of the newborn. In all of these, improvement with drug therapy was prompt and satisfactory. Aside from the case of staphylococcal peritonitis mentioned previously, there was only one case of severe staphylococcal infection in this series. The patient had a deep iliac adenitis and was given large doses of sulfamerazine for nine days during which time he remained toxemic and febrile; improvement did not begin until the area of suppuration was surgically drained.

The remaining cases included catarrhal and suppurative otitis media, a variety of upper respiratory infections, acute laryngotracheobronchitis, bronchiolitis, cervical adenitis, and certain other infections in which it was impossible to evaluate the effectiveness of sulfamerazine. On several occasions the drug was given prophylactically in connection with surgical procedures to patients with rheumatic fever and to patients with intussusception, strangulated hernias, and tracheobronchial foreign bodies, for the purpose of minimizing any complicating infection.

THE TOXIC EFFECTS OF SULFAMERAZINE

Each patient in this series was carefully observed for possible toxic reactions. Many of the infants and children were treated for periods of not longer than one week, so that those reactions which ordinarily occur late were rarely encountered. Sodium lactate was given to each patient either orally or parenterally in an attempt to render the urine alkaline. For this purpose, 5 c.c. of a one molar solution per kilogram body weight per twenty-four hours were given orally in either four or six divided doses.¹¹ For those patients receiving sulfamerazine subcutaneously, sodium lactate was incorporated into the subcutaneous infusion in a dosage of 30 c.c. of 1/6 molar solution per kilogram body weight per twenty-four hours. This quantity usually has been found sufficient to keep the urinary pH above 7.0. We prefer sodium lactate to sodium bicarbonate because it does not produce gastric distress, it is easily administered to small infants and can be incorporated readily into any subcutaneous or intravenous infusion fluid.

We have divided the patients into two groups with respect to the level of sulfamerazine attained in the blood, the dividing line being a concentration of 15 mg. per cent, and have listed in Table II the toxic reactions occurring in each group. One hundred and twelve of the patients had blood levels less than 15 mg. per cent. In the other twenty-three patients, because of the severity of their

TABLE II

TOXIC EFFECT	LOW BLOOD LEVEL GROUP (112 CASES)		HIGH BLOOD LEVEL GROUP (23 CASES)		TOTALS	
	NO.	%	NO.	%	NO.	%
Fever	4	3.6	1	4.4	5	3.7
Rash	4	3.6	0	0	4	3.0
Rash and fever	2	1.8	0	0	2	1.5
Leucopenia	0	0	4	17.4	4	3.0
Anemia	0	0	1	4.4	1	0.7
Anorexia	1	0.9	0	0	1	0.7
Vomiting	1	0.9	0	0	1	0.7
Transitory microscopic hematuria	9	8.0	3	13.0	12	8.9
Microscopic hematuria	13	11.6	4	17.4	17	12.6
Gross hematuria	2	1.8	0	0	2	1.5
Oliguria and albuminuria	0	0	1	4.4	1	0.7

infections, an effort was made to maintain the blood levels between 25 and 30 mg. per cent with an observed range of from 15 to 50 mg. per cent.

Drug fever and rash were of the same general character as those seen with sulfadiazine. The rash was macular and erythematous in character, of varied distribution, and disappeared promptly when the drug was discontinued.

Leucopenia (total white cell count below 4,000 c.mm.) developed gradually in each of the four cases listed. The percentage of polymorphonuclear cells did not drop below 18; in two instances the leucocyte count rose gradually to normal although the drug was continued, while in the other two the drug was stopped. In no instance could the reaction be called a true agranulocytosis. In the one patient in whom anemia was observed, the hemoglobin dropped to 9.5 Gm. per 100 c.c. The anemia was corrected by blood transfusion and did not recur despite the continuance of the drug.

In infants and children, anorexia and vomiting often occur in the presence of infections, and it was not possible to determine to what extent these effects might have been due to the drug. In only two patients were anorexia and vomiting thought to be due to the administration of sulfamerazine, and in general the drug was extremely well tolerated.

Whenever possible, daily urinalyses were done in an effort to detect and to determine the extent of any renal complication which might occur from sulfamerazine. As already mentioned, all of the patients were given sodium lactate in an attempt to keep the urine alkaline. Crystals of sulfamerazine, both the free and acetylated forms, were seen frequently in the urinary sediment, but no attempt was made to determine the frequency with which crystalluria occurred. Nine per cent of the total group exhibited mild transitory microscopic hematuria. Such microscopic hematuria is fairly common in sick infants and children, and it is impossible to say that this finding was due to the drug rather than to the infection for which the patient was being treated. Twelve and six-tenths per cent of the patients exhibited microscopic hematuria of such degree and duration as to be classed as a true renal reaction to sulfamerazine. The reaction occurred somewhat more often in those patients receiving large doses of drug rather than in those receiving smaller amounts. Whenever such hematuria oc-

curred, measures were instituted to increase the alkalinity and the volume of the urine with resultant clearing of the urine on each occasion.

Gross hematuria occurred only twice in this series, both of the patients being in the "low blood level" group. In one the urine was definitely alkaline to litmus and in the other acid. Hematuria subsided in each instance after withdrawal of the drug and the administration of fluids and sodium lactate. In one patient in the "high blood level" group definite oliguria developed, and the urine showed 1 plus albumin by the heat and acetic acid test but no other abnormalities. The albuminuria ceased, and adequate urine flow was quickly established when fluids were administered intravenously.

On no occasion in this series were any of the more serious renal complications such as anuria, renal colic, or toxic nephrosis noted.

Sulfamerazine was administered to six patients with nephritis for periods ranging from three to twenty-seven days for the purpose of treating complicating infections. In no instance could we detect evidence that the drug tended to accentuate the pathologic process in the kidney. It is important to remember in using the drug in patients with impairment of renal function that it may be necessary to reduce the dosage appreciably in order to avoid excessively high levels in the blood.

COMMENT

From this study it is evident that the principal advantages which sulfamerazine offers over the other commonly used sulfonamide drugs in treating infants and children are that satisfactory blood concentrations can be produced by a smaller total daily dosage of the drug and that the doses may be given at less frequent intervals. The hope that, because of rapid absorption of the drug from the gastrointestinal tract, the parenteral route for the administration of sulfamerazine to infants and children could be dispensed with in many instances has not materialized. Our data show clearly the need for parenteral administration when high blood concentrations are desired quickly, and we feel that the subcutaneous route is the one of choice.

As far as therapeutic effectiveness is concerned, it is apparent that this series of cases is not large enough to warrant a statistical comparison of the effectiveness of sulfamerazine with that of sulfapyrazine, sulfadiazine, and sulfathiazole. However, it is our definite impression that it is as valuable as are the others.

From the standpoint of toxicity in infants and children, sulfamerazine offers no advantage over sulfadiazine and appears to be somewhat more toxic than sulfapyrazine.¹³ The reactions encountered in this series were mild, there being none which could be classed as serious. In view of the routine use of sodium lactate, it is surprising that microscopic hematuria occurred so frequently in this series. Gross hematuria occurred in only two patients and albuminuria and oliguria only once. Whether these renal complications would have occurred more often had alkali not been administered concurrently is difficult to say.

SUMMARY

A study of the absorption, methods of administration, therapeutic effectiveness, and toxicity of sulfamerazine in an unselected group of 135 infants and children with infections revealed the following pertinent data:

1. Sulfamerazine is rapidly absorbed from the gastrointestinal tract and rather slowly excreted by the kidney. Accordingly, adequate blood concentrations are easily attained by the oral administration of 0.05 Gm. per kilogram of body weight every eight hours (three-quarters of the total daily dosage usually employed with sulfathiazole and sulfadiazine). Sulfamerazine thus possesses an advantage over the other sulfonamide drugs in that they must be given in larger total dosage with more frequent doses to attain comparable blood levels.

2. High blood concentrations are easily and rapidly produced by the subcutaneous administration of sodium sulfamerazine. The absorption of sulfamerazine from the gastrointestinal tract, although more rapid and complete than is the absorption of the other sulfonamide drugs, does not lead to values sufficiently high to obviate the need for parenteral administration of the drug when very high values are desired.

3. Sulfamerazine was observed to pass into the spinal fluid to the extent of from 52 to 83 per cent of the whole blood value and 41 to 73 per cent of the plasma value, while the concentration in pleural and ascitic fluid equaled that in the plasma.

4. From a purely clinical evaluation, the therapeutic effectiveness of sulfamerazine is entirely comparable to that of sulfapyrazine, sulfadiazine and, sulfathiazole.

5. The toxic reactions encountered were relatively frequent but, for the most part, were mild, and no serious reactions occurred. On the basis of our past experience, the frequency of toxic reactions was definitely greater with the use of sulfamerazine than with sulfapyrazine and certainly as great as with sulfadiazine.

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THE PREVENTION OF EDEMA IN INFANTS UNDERGOING SULFONAMIDE TREATMENT

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IT HAD been noted for some time at the Children's Hospital that infants treated with sulfonamides and adjuvant alkalies became edematous more often than might be expected from the incidence of pulmonary infections. Upon closer examination it was noted that even in the absence of frank pitting edema, many other infants made precipitous and appreciable weight gains, which were as rapidly lost upon recovery and cessation of therapy. It has long been a well-recognized observation that patients with pneumonia very frequently became edematous and a diuresis was hailed as the first sign of recovery. However, with the advent of the sulfonamides this was noted more often in pulmonary infections and also, interestingly enough, was seen in other infections. The alkali in general use in the Children's Hospital, as elsewhere, was sodium bicarbonate.

Because of the well-known importance of the sodium ion in water balance, it was decided to see whether the edema could be prevented by using alkalies with cations other than the sodium ion. Potassium citrate was chosen because of its high solubility and availability at the time. Without selection, alternating admissions requiring sulfonamide therapy were given either sodium bicarbonate or potassium citrate.

The dosage of the sodium bicarbonate ranged from 0.28 to 0.42 Gm. per kilogram. The dose of potassium citrate ranged between 0.44 to 0.70 Gm. per kilogram. In the administration of the drugs the larger doses were given the smaller infants. After this series, a group of children were given a mixture of sodium bicarbonate and potassium citrate. This mixture contained .066 Gm. of potassium citrate and .033 Gm. of sodium bicarbonate in each cubic centimeter. The average dose was 0.42 Gm. of potassium citrate and 0.21 Gm. of sodium bicarbonate per kilogram of body weight. This mixture was used in an attempt to lessen the theoretical chances of toxicity due to the potassium ion and at the same time to obviate the production of edema due to excess sodium. A fourth group was given 10 per cent sodium lactate in dosage of 0.48 Gm. per kilogram of body weight as the alkalinizing agent. The apparent discrepancies in amount of alkali used do not really exist. This is made clear by stating the dosage in moles of cation used per kilogram of body weight. Examples of this are given in Table I. All the alkalies were given by mouth. Very few children were unable to take them in this manner. These infrequent patients are customarily given parenteral one-sixth molar sodium lactate. The pH of the urine was measured with nitrazine paper three times a day. All the alkalies tried, in the dosages given, satisfactorily kept the pH of the urine between 7 and 7.5 or better,

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as measured by the nitrazine paper method of testing pH. The shortcomings of this method are well known but do not need to concern us here.

No evidence of potassium intoxication was noted on electrocardiograms of four of the patients given potassium citrate. None of the infants gave evidence of any sulfonamide damage to their kidneys.

Only those patients who had frank pitting edema as well as marked sudden weight gains were classified as edematous. The number of infants given each alkali and the number of each group that became edematous are given in Table I. Of those that became edematous three were diagnosed as having bronchopneumonia or interstitial pneumonia; two had bronchiolitis; one had influenza; two had meningitis; one had roseola infantum; and the other two had pyrexia of unknown origin as their initial diagnoses. The final diagnoses of the last two were neurological disorders.

TABLE I

DRUG	NO. PATIENTS	NO. PATIENTS WITH EDEMA	AVERAGE DOSE PER KILOGRAM OF BODY WEIGHT	MOLES OF CATION
				PER KILOGRAM WEIGHT
NaHCO ₃	23	6	0.28-0.42 Gm.	.0033-.005
Na lactate	11	2	0.48 Gm.	.0043
TOTAL	34	8		
NaHCO ₃ and K citrate	23	3	0.42 Gm. of K citrate and 0.21 Gm. of NaHCO ₃	
K citrate	31	0	0.44-0.70 Gm.	.004-.006

In more than one-half of the patients who developed edema, the edema developed at a time when the pH of the urine was below 7.0. Generally, with the subsidence of edema the urine would become alkaline. The edema would reach its peak in from one to two days. The patient frequently gained as much as a pound in this period and then would gain little or no more. As a rule, there would be little fluctuation in weight after the initial precipitous rise till the subsidence of the edema. The loss in weight generally was rapid, requiring from three to five days. In one instance, the edema disappeared while the patient was still on the sodium-containing alkali; in the rest it did not disappear until the alkali was omitted with or without potassium citrate being substituted for it. It is not known what the diuretic effect of the potassium was, because urinary collections for volumetric determinations are so difficult in infants. No attempt was made to determine the effect of the potassium alkali on the level of sulfonamide in the blood since there are so many variables, such as speed of absorption and time of collecting blood sample in relation to time of administration, that govern the blood level of sulfonamide. However, Peterson, Goodwin, and Finland have shown that the pH of the urine is probably more important than the volume in determining the amount of excretion of sulfonamide.¹

No advantage for potassium citrate was noted in older children as clinical edema has not been a problem here. Its use as adjuvant therapy with sulfonamide treatment of infections occurring in cases of the nephrotic syndrome is obvious. It should be stated, however, that its value seems to be entirely a negative one. That is, it does not add to the edema as does sodium bicarbonate.

On the other hand, it does not seem to have any diuretic action in nephrosis although it has been tried in large doses in the past. In fact, nephrotic children occasionally have had a diuresis after potassium citrate is stopped. This may well have been due to cessation of sulfonamide therapy and recovery from infection which were coincident to stopping potassium citrate administration. This last is further borne out by one nephrotic patient who was given potassium citrate alone and did not have the response that was seen when this drug was administered to similar patients with sulfonamides in the presence of infection.²

Potassium bicarbonate has also been used with sulfonamides in the treatment of infections in the presence of congestive failure by Ohnysty and Wolfson.³

Nephritis, nephrosis, and other kidney diseases per se are not contraindications to the use of potassium-containing alkalis, but it cannot be emphasized too strongly that anuria is a contraindication. Although the amounts of potassium ion administered in the two cases reported by Finch and Marchand⁴ were far in excess of the ordinary dosage reported here, these two cases of potassium poisoning in anuria show the possible dangers in cases of anuria.

Thus, it would seem that the substitution of alkalis containing the potassium ion instead of sodium as the cation results in a significant lessening of the incidence of edema. It would seem reasonable to believe that the added burden of edema from sodium retention due to the use of sodium-containing alkalis might prove embarrassing to the patient.

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INCIDENCE OF REACTIONS TO SULFONAMIDE DRUGS IN INFANTS AND CHILDREN

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A REVIEW of the literature¹⁻¹⁸ on toxicity associated with sulfonamide administration reveals the average incidence to be about 5 per cent among patients of all age groups. Some reports² place the incidence of toxic reactions as high as 25 per cent; other reports⁴ describe it in only 2 per cent of the cases studied. This paper deals with observations on the frequency and character of such reactions in more than 5,000 infants and children receiving sulfonamide drugs on the wards of the Children's Hospital of Michigan during a period of two and one-half years from 1942 to 1944. Chemotherapy was so extensively used at this time that the total number of 5,000 is based not on actual count but upon extension of statistics covering sample periods scattered throughout the whole two and one-half years. The figure is considered to be a conservative estimate. During this period of observation and in this number of administrations, sixty cases of drug fever (twenty-five with accompanying rashes), two cases of malignant neutropenia, two cases of hemolytic anemia, and four cases of anuria were encountered. Thus, the total incidence of important complications in this series was sixty-eight, or less than 1.4 per cent of the children treated. Statistical data on hematuria as a renal complication were also compiled for a survey period of one year, during which time over 1,500 patients received sulfonamide therapy. Significant renal disturbances occurred in ten instances, or less than 1 per cent of these cases.

Most of the patients studied received sulfadiazine. Early in the series some patients received sulfathiazole, and during one six-month period sulfamerazine was used extensively. The usual dosage of sulfadiazine and sulfathiazole employed was $\frac{1}{2}$ grain (32 mg.) per pound (454 Gm.) as an initial dose, and a maintenance dosage of 1 grain (64 mg.) per pound per twenty-four hours, divided into four or six equal doses. The sodium salt was used for parenteral and occasional oral administration in slightly smaller dosage. The maintenance dosage of sulfamerazine was from $\frac{1}{2}$ to $\frac{3}{4}$ grain (32 to 48 mg.) per pound per day.

TYPES OF UNTOWARD REACTIONS

The types of untoward reactions observed are grouped for convenience according to the effects produced by the drugs on the various body systems and the body in general (Table I).

1. *Gastrointestinal*.—As nausea and vomiting so frequently accompany acute illness in children it was not always possible to determine whether such manifestations resulted from the disease or the drug. However, it was the rule

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Much of the sulfadiazine and sulfamerazine used in this study was generously provided by the Lederle Laboratories, Pearl River, N. Y.

TABLE I. UNTOWARD REACTIONS TO THE SULFONAMIDES

-
1. *Gastrointestinal*.—Nausea and vomiting (first to second day of administration)
 2. *Renal*.—Hematuria, oliguria, anuria (first week)
 - a. mechanical obstruction by crystals
 - b. toxic
 3. *Neurologic*.—Mental disturbances (first to second day)
 4. *Blood and blood-forming organs*.—Leucopenia, anemia, hemolytic anemia, jaundice, purpura (first to second week)
 5. *Systemic*.—Fever, with or without rash, occurring alone or in combination with any of the above reactions
 - a. *Initial administration*: Fever with or without rash (fifth to ninth day)
 - b. *Subsequent administration*: Fever usually with rash (first twenty-four hours)
-

to find that the gastrointestinal disturbances disappeared as the illness was brought under control, despite continuation of sulfonamide therapy. No vomiting occurred in any of the children receiving sulfonamides at a time when they were free from disease. Whenever vomiting from any cause interfered with oral administration, parenteral routes were found quite satisfactory and in many instances were the preferred methods of administration.

2. *Renal Complications*.—Renal reactions such as hematuria, oliguria, and anuria comprise over 50 per cent of the reported cases of drug reaction in the literature.^{1-3, 19-32} Two main types of renal reactions have been described.^{23, 24, 29, 30} In the one, the process is apparently mechanical; crystals, usually of the less soluble acetylated forms, cause bleeding by irritation of the renal endothelium, or plugs of crystals obstruct the kidney tubules or even the ureters. In the second type, the drug produces toxic effects on the kidney parenchyma; histologically areas of focal necrosis are seen along with degenerative changes in the tubules. These changes may be accompanied by similar necrotic changes in other organs and have been thought by some writers to be evidences of drug sensitivity.^{21, 29, 34-36} Significant parenchymal damage to the kidney was not found in over 300 autopsies on children who received sulfonamides prior to death, and in only one case was there severe diffuse degenerative change in the tubules.*

In general, untoward effects of drug therapy upon the kidney have proved much less troublesome in children than in adults. As already stated, only for the last twelve-month period of this study are statistics available on the occurrence of gross hematuria. Over 1,500 children received sulfonamides during this time, and of this number ten showed gross hematuria (0.6 per cent). Microscopic hematuria was infrequently observed, and in only a few patients did it seem necessary to discontinue the drug because of this latter occurrence. The presence of sulfonamide crystals alone in the urine was not considered a reason to discontinue the drug.

Hematuria, when encountered, was seen most frequently during the first two or three days of therapy when larger than usual doses were given over a short period of time. Whenever microscopic hematuria was discovered, the drug was either temporarily discontinued for one or two doses, or the dosage reduced and fluid intake increased orally or parenterally. Drug treatment was then

*Dr. W. W. Zuelzer examined all pathologic material.

continued in the absence of further complications. In the presence of gross hematuria or the continuance of microscopic hematuria despite the measures stated, drug administration was always stopped. If resumption of the drug was considered necessary, smaller dosage was employed and large amounts of fluids were given usually with success. The occurrence of hematuria alone does not preclude re-employment of the drug in subsequent infections.

The development of oliguria and anuria, either preceded or accompanied by hematuria, was considered a danger signal calling for immediate cessation of drug therapy. During the entire period of observation, four cases of actual anuria were encountered. Two of these responded to therapy and recovered without any apparent permanent kidney damage; both of the remaining cases were fatal. In both of the latter instances sulfathiazole had been employed. One child, 5 years old, died in uremia after nine days of treatment with the usual 1 grain per pound per day dosage. The autopsy disclosed many congenital urinary anomalies with secondary obstruction and hydronephrosis. Accumulations of sulfonamide crystals were found blocking the calices and ureters. The second child, 11 months old, also showed at autopsy ureters completely blocked by plugs of crystals. He had received 1 grain per pound per day dosage for seven days. In both of the anuric cases with recovery (patients aged 11½ and 10 years), ureteral catheterizations were performed. In neither case was any obstruction encountered, but in each a small amount of syrup-like, bloody urine was obtained from the kidney pelvis. No crystals were found on microscopic examination of the urine. Despite the absence of obstruction, the catheters were left in place and shortly afterward urine flow began, so that the procedure may have been beneficial. Thus, it is of interest that the two fatalities seemed to be traceable to mechanical blockage, while the two cases with recovery were not proved to be obstructive. No child died as a result of renal damage from sulfadiazine or sulfamerazine.

Therapy in renal complications has thus been directed toward reducing the concentration of the drug in the urine and insuring an adequate urinary flow. In infants, a fluid intake of 2½ to 3 ounces (75 to 90 c.c.) of fluid per lb. per day was considered necessary. Older children received 40 to 80 ounces (1,200 to 2,400 c.c.) of fluid daily. Because of the marked infrequency of kidney complications in this series, it has not been thought necessary to supplement therapy by the routine administration of alkali.¹⁵ The use of alkali in pediatric patients introduces difficulties in forcing children to take the relatively large amounts of soda (10 to 20 Gm. daily) needed to render the urine effectively alkaline.^{20, 37} In addition, the tendency of alkali medication to produce refusal of oral fluids argues against the routine use of alkaline drugs.

3. *Neurologic*.—What part the sulfonamide drugs play in the production of mental disturbances is difficult to assess, since in the early stages of acute illness children often display drowsiness, increased irritability, confusion, and even delirium. These evidences of central nervous system disturbance tend to clear up with improvement in the child's condition, even though drug administration is continued. In only two instances was it necessary to discontinue the drug because of delirium. Severe neurologic disturbances such as polyneuritis and optic atrophy were not encountered.

4. *Blood and Blood-Forming Organs.*—The incidence of leucopenia (white blood cell count below 5,000 per cubic millimeter) is variously reported as between 2 per cent and 3 per cent.^{1, 4, 10, 22, 24, 48} Whenever marked leucopenia (3,500 or less) was observed in this study, drug fever and rash were usually present also, indicating a sensitivity reaction. Leucopenia of this degree was rarely seen, and in eight cases in which serial counts were made, discontinuance of drug therapy resulted in a rapid rise of white cells. Two cases of malignant neutropenia were observed; in both, cells of the granulocytic series almost entirely disappeared from the blood. The subjects were infants who had been receiving sulfonamides for several weeks. With cessation of drug therapy and the employment of blood transfusions, neutrophilic cells reappeared and the white blood cell count was gradually restored to normal. Counts of 4,000 to 5,000 white blood cells per cubic millimeter were not considered an indication for stopping the sulfonamides, since most such counts returned to normal even though drug therapy was continued. In these instances, daily counts were recommended, and if the leucopenia progressed under such observation the drug was then discontinued.

Relatively few cases of hemolytic anemia due to sulfadiazine have been reported by others.²⁹ Two cases occurred in this series (both accompanied by fever). In these children symptoms began on the second and third days of drug administration, respectively. Drug therapy was discontinued and blood transfusions were given, with prompt recovery. Jaundice was present in these two patients but was encountered in no others. In no other patient were signs of hepatic insufficiency demonstrated. Purpura developed in one patient, but whether or not it was due to drug therapy could not be definitely ascertained. It can, therefore, be concluded that serious hematologic complications of sulfonamide therapy are infrequent in infants or children. When they do occur, other evidences of toxicity, such as fever and rash, are usually present as well.

5. Systemic Effects.—

A. *Initial Administration:* The occurrence of fever, with or without rash, generally indicates the development of what may be termed a toxic reaction. However, this does not necessarily mean that the patient has acquired permanent sensitivity to the drug, as will be shown. The reports of other authors indicate the incidence of any fever to be from about 2 to 10 per cent.¹⁻¹⁸ In this study sixty febrile reactions were encountered, an incidence of 1.2 per cent. Twenty-five of these patients had accompanying rashes.

The term "febrile reaction" indicates the development during drug administration of a temperature elevation which cannot be satisfactorily explained

TABLE II. TOXIC FEBRILE REACTIONS TO SULFONAMIDES

TOXIC FEBRILE REACTIONS	SULFADIAZINE	SULFATHIAZOLE	SULFAMEERAZINE
No. cases fever alone	27	7	1
No. cases fever with rash	19	6	0
Total no. febrile reactions	46	13	1

(These figures do not represent a comparison of the toxic effects of the various drugs. Since most of the patients were given sulfadiazine, the larger number of reactions occurred in this group.)

on the basis of the disease and which subsides after the drug is discontinued. It is obvious that not all such fevers are due to drug reactions, and that therefore the figure given may be in excess of the actual frequency.

Fever ascribed to the sulfonamide drugs generally began toward the end of the first week of therapy or during the second week, and persisted until the drug was stopped. The elevated temperature then usually fell abruptly or came down slowly over a period of forty-eight hours, and in all cases complete recovery followed. In a few cases, fever which did not develop until shortly after cessation of drug therapy was suspected of being of drug origin, but readministration of the drug never produced a second febrile reaction.

The rash, which was observed in almost one-half of these febrile reactions, usually appeared while the temperature was rising or shortly afterward. Skin eruptions occurring in the absence of fever were never proved to be of drug origin. Scarlatiniform or measleslike eruptions were most often seen. Diffuse redness of the pharynx often accompanied the rash and caused complaints of sore throat or difficulty in swallowing. The absence of exudate over the tonsils and the diffuseness of the enanthem helped to distinguish the reaction from scarlet fever, but in some instances the differentiation at first was quite difficult. Leucocytosis, with counts as high as 70,000, and with the percentage of polymorphonuclear cells over 90 per cent, was not unusual during the febrile episodes. Some cases showed moderate leucopenia. In all instances, the counts rapidly returned to normal after the drug was stopped. Only one case of a toxic reaction resulting from local drug application was met with in this series, despite frequent use of the drug for many types of skin infection. Exfoliative dermatitis and other severe dermatological conditions were not encountered.

B. Repeated Administration: In a previous paper Fink and Wilson¹³ showed that there is little evidence of increased incidence of reactions in children during a second or subsequent course of the drug. Although several other authors have not confirmed this,^{12, 39, 40} the majority of the reports^{1, 3, 4, 6, 13, 17, 18} agree that a second course is not more toxic than the first. The material of the present study has not indicated a significant effect of one course of uncomplicated sulfonamide administration in sensitizing the patient against later administration of the same drug. However, patients who have shown a febrile reaction to a drug administered once are likely to have developed sensitivity to that drug and may react with fever and rash to its readministration.^{11, 13, 38} This type of reaction develops almost always within forty-eight hours after a repeat dose and has been termed an "immediate" or hypersensitivity reaction. During the period of two and one-half years of this study, every patient who developed this "immediate" type of reaction had also shown a febrile reaction to a previous course of the drug. Apparently, then, the original temperature elevation may indicate the development of sensitivity. Consequently, if a complete history fails to disclose an earlier febrile reaction, a child cannot be considered sensitized, and second and subsequent courses then can be given without fear of an immediate reaction.

In an attempt to determine whether or not febrile reactions always mean the establishment of sensitivity, thirty-four children who showed otherwise

TABLE III. REACTIONS TO REPEAT DOSES OF SULFONAMIDES

	INITIAL REACTION— FEVER ONLY				INITIAL REACTION— FEVER AND RASH				GRAND TOTAL
	SULFADIAZINE	SULFATHIAZOLE	SULFAMERAZINE	TOTAL	SULFADIAZINE	SULFATHIAZOLE	SULFAMERAZINE	TOTAL	
Total number cases retested with drug producing fever	9	3	1	13	18	2	1	21	34
No reaction to test dose	5	2	1	8	5	2	1	7	15
Immediate reaction fever only	3	0	0	3	0	0	0	0	3
Immediate reaction fever and rash	1	1	0	2	13	1	0	14	16
Total immediate (hypersensitivity) reactions	4	1	0	5	13	1	0	14	19

unexplained temperature elevation during initial courses of one of the sulfonamides were deliberately given repeat courses. The usual test dose was 0.25 Gm. (grains 3.8) given orally. If no reaction occurred to the first repeat dose, the drug was in most instances administered for forty-eight to seventy-two hours, if necessary. Most of the tests were performed within two weeks of the original reaction.

In thirteen of the thirty-four children thus tested a rash had not been observed during the original febrile reaction. Of these thirteen children, eight showed no untoward response to the test exhibition of the same drug, and these children were therefore not considered to have become sensitized to the drug. Only two reacted with fever and rash, while three showed fever only.

Of the twenty-one children who had shown fever and rash at the original reaction, only seven showed no response to the test doses. All of the remaining fourteen quickly developed both fever and rash. All the children responding with fever and rash did so within eight hours after the test was given. Those responding with fever alone did so in from twenty-four to forty-eight hours.

It would therefore appear that slightly over one-half of the children showing febrile reactions to sulfonamide drugs may coincidentally be sensitized to the drug, as manifested by the production of an "immediate" type of response on readministration. If the initial fever is accompanied by rash, the chances of sensitization are even greater.

Test doses of a different sulfonamide were given in nine instances to seven children. Five of the children reacting to test doses of sulfadiazine were tested with sulfathiazole. Two developed reactions. One of these was given sulfamerazine without eliciting any response, and the other received sulfapyridine without reaction. Two children reacting to sulfathiazole did not show any untoward effect from sulfadiazine administration. Further work is necessary to determine how much cross-sensitization can occur, but apparently a different sulfonamide is less likely to produce a reaction than the original one in sensitized children.

From these observations, it is concluded that sulfonamides can be safely readministered to children who have shown no previous reactions; whereas if a

child has once shown a toxic reaction, the probability is that subsequent administration will produce further and more immediate difficulty. Under such circumstances a different sulfonamide may be tried if readministration of a sulfonamide is considered therapeutically essential, as there is some evidence that it may be better tolerated. A test dose of 0.25 Gm. (grains 3.8) will usually reveal the presence of sensitivity. In the event of cross-sensitization, the use of sulfonamides must be abandoned, and other therapeutic agents such as penicillin should be used where effective.

OBSERVATIONS ON SULFONAMIDE SENSITIVITY

Merkel and Crawford,²³ Lederer and Rosenblatt,²⁴ Geever,²¹ and others have all reported findings on patients dying as the result of sulfonamide administration. Most of the deaths were of renal origin, but a majority also showed toxic febrile reactions, along with the renal reactions. The outstanding finding in all cases was the presence of areas of focal necrosis in the kidney, as well as in the liver, spleen, lungs, brain, and heart, indicating widespread damage. Rich³⁴⁻³⁶ has found similar areas of necrosis in his study of autopsy material. However, his findings were made not only on patients receiving sulfonamides without reaction, but also on patients who had received horse serum but whose deaths were not due to any serum reaction. Rich has demonstrated that the areas of necrosis are the result of periarteritis nodosa-like lesions which he believes may be manifestations of sensitivity, not only to sulfonamides but also to serum, bacterial protein, and the like. The lesions are analogous to those in the commonly observed Arthus phenomenon.

French and Weller,⁴¹ in a review of 283 autopsies on patients who had received sulfonamide drugs but in whom death had not been due to drug toxicity, found interstitial myocarditis in 126 cases. Rich has postulated that such changes are similar to those of periarteritis nodosa. The significance of these observations is not quite clear, and further reports will be awaited with much interest. In autopsy findings in more than 300 patients who had received sulfonamides at the Children's Hospital of Michigan, no instance of significant interstitial myocarditis has been found, and in no case has the presence of areas of focal necrosis been demonstrable.

Several investigators⁴²⁻⁴⁶ have reported the results of experiments attempting to explain the mechanism of sensitization. Wedum,^{42, 43} and Gerber and Gross⁴⁵ have demonstrated that experimental animals can be sensitized to protein conjugated with sulfonamide. By using the conjugated protein as the antigen, they have elicited positive skin reactions in experimentally sensitized animals and have produced anaphylactic shock by its intravenous injection. Use of the unconjugated sulfonamide failed to produce a reaction in animals, and attempts to produce skin reactions in sensitized human beings were unsuccessful. However, Leftwich⁴⁷ reported that by using blood serum from patients receiving sulfonamide drugs, and therefore containing protein-bound sulfonamide, he could produce positive skin tests in sensitized patients. Burton, Wheeler, and one of us⁴⁹ have been unable to elicit positive skin tests in children by this method. At present, we believe that the only certain way to demonstrate sensi-

tivity among pediatric patients is by observing the effects of oral readministration of the drug: A test dose of 0.25 Gm. (grains 3.8) is generally sufficient to produce a reaction in a truly sensitized child.

SUMMARY

In a study of more than 5,000 infants and children receiving sulfonamide drugs on the wards of the Children's Hospital of Michigan during a period of two and one-half years from 1942 to 1944, the following observations were made:

1. Sulfonamides may produce or aggravate gastrointestinal and neurologic disturbances in acutely ill children. Such reactions were rarely noted in children receiving chemotherapy during convalescence or at a time when they were well.

2. Renal complications were rare and apparently less frequently encountered than in adults. Two deaths from anuria not associated with crystalluria occurred in this series.

3. Untoward effects on the blood and blood-forming organs were also uncommon in children and when present were usually associated with evidences of a general reaction such as fever and rash. Two cases of malignant neutropenia and two cases of hemolytic anemia were encountered; all patients recovered.

4. Sixty patients (1.4 per cent) developed febrile reactions, twenty-five with accompanying rashes. Leucocytosis with white blood cell count as high as 70,000 often occurred during the reaction, although leucopenia was occasionally seen. All patients completely recovered following cessation of drug therapy.

5. Over one-half (59 per cent) of the patients reacting to one course of sulfonamide developed "immediate" reactions to tests with repeat doses. Test doses of 0.25 Gm. (grains 3.8) were usually sufficient to produce a reaction.

6. "Immediate" reactions were observed only in those patients who had shown previous drug reactions.

7. Seven children were given test doses of a sulfonamide different from that to which they were proved sensitive. Only two developed reactions, and both of these received a third sulfonamide without reaction.

8. Observation of the patient after oral administration of a test dose of 0.25 Gm. (3.8 grains) of sulfonamide is recommended as a test for suspected drug sensitivity.

9. Skin testing of suspected sulfonamide sensitive patients with human sulfonamide-containing serum after the manner of Leftwich has not proved useful in children.

CONCLUSIONS

Untoward reactions to sulfonamides are infrequent in infants and children and rarely cause serious effects. Such patients are apparently not easily sensitized. Since danger of severe reaction to subsequent sulfonamide administration exists only when a febrile reaction has occurred previously, there is apparently no greater reason to fear harmful effects from multiple courses of drug therapy

than from the first course. Because of the low incidence of toxic reactions, sulfonamides should not be withheld from infants or children because of fear of producing an untoward response.

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TABLES FOR PREDICTING ADULT HEIGHT FROM SKELETAL AGE AND PRESENT HEIGHT

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BEING exceptionally tall or short, in comparison with other children the same age, is often a matter of concern for children or their parents. For this reason the extent of epiphyseal closure is often investigated roentgenographically in order to determine likelihood of future growth and to estimate the extent to which further growth may occur. In a more limited field, surgeons have been interested in such estimates, in predicting the effect of growth in certain forms of osteotomy. Recent studies carried out at the University of California on the relation of growth to skeletal age indicate that it is possible to estimate, within certain limits of error, the probable adult height of children whose growth is still incomplete.¹

Individual differences in velocities of maturing result in widely varying degrees of maturity among any random sample of children the same age, especially during adolescence. But velocities of maturing are not simply related to growth in size.² Children who mature early follow a different course of growth than children who mature late. Furthermore there are sex differences in the patterns of growth of early and late maturers. In general, for both sexes, there are two factors which influence growth. (1) During childhood, the mere differences in velocity of maturation make the rapid maturers large for their age and the slow maturers small. But (2) the longer the period of time a person is in the process of growing (that is, epiphyses open and healthy growth factors operating), the more opportunity he has for growth. Therefore, though slow maturers are small for their age, they tend, actually, to be large for their skeletal age, while the rapid maturers, though large for their chronological age, tend to be small for their skeletal age.

In girls some factor, probably related to the female sex hormones, stops growth rather abruptly after menarche. As a result we find that early maturing girls are usually large when young, slowing down to about average in height at 13 years, and completing their growth rapidly, to become small adults. Late maturing girls, conversely, are more often small when young, catch up to the average at about 13 and become tall adults.

Early maturing boys do not exhibit this abrupt curtailment of growth but slow down more gradually, and they seem to have a normal likelihood of becoming tall, or average, or short adults. Late maturing boys continue to grow, some even into their early twenties, and more often than not they become tall adults. Because of further differences in body build of early and late maturing boys, the late maturers, while young, are at a considerable disadvantage, physically: the early maturers tend to be large and broad-built or heavy-set at all ages, while the late maturers are usually slender and long-legged, their greater adult height being due primarily to continued growth of the legs.

From the Institute of Child Welfare, University of California.

Because of these characteristic differences between children growing at different velocities, predictions of their adult height will be more nearly accurate if determined for each group separately.

Tables designed to facilitate estimates of adult height are presented here, for boys and girls, between the ages of 7 years and maturity. These tables are constructed from data from two sources, Massachusetts children observed in the Harvard Growth Study* and the California children studied at the Institute of Child Welfare of the University of California.

To secure a measure of relative growth each child's height at any given time was expressed as a percentage of his own adult stature as measured after closure of the epiphyses of the bones in his hand, wrist, and knee.† When this was done, the per cent of mature height attained was found to be very closely related to skeletal age as determined by the Todd standards.³ This relationship to skeletal age was found to be much closer than to chronological age. It is reasoned, therefore, that if we wish to predict adult height, the prediction will be much more accurate if a child's skeletal age is taken into account in making the estimate. This is especially true during the early teens when differences in physical maturity contribute so largely to differences in children's heights. In using these tables, it must be remembered that this system of predictions is based on measurements of normal children. We cannot expect it to be applicable to cases of extreme deviation in which the regulators of growth are not functioning normally.

The tables have been constructed to facilitate the process of computing predicted height. In order to predict a child's mature height it is necessary to have an assessment of his skeletal age (based on x-rays which have been compared with standards such as those of Todd³ or Flory⁴), and his height, measured at the time the x-rays were taken. For the younger ages it is necessary, in addition, to have the child's chronological age, because age must be taken into account when a child is retarded or accelerated in a marked degree. Therefore, separate tables have been constructed for children under twelve years who deviate widely from their age norms.

DIRECTIONS FOR USING THE PREDICTION TABLES

First, select the correct table for the child's sex, skeletal age, and degree of acceleration or retardation. (Because girls mature more rapidly than boys, the difference during adolescence amounting, on the average, to two years, it is

*Shuttleworth, F. K.: Data on the Growth of Public School Children (From the Materials of the Harvard Growth Study) *Monographs of the Society for Research in Child Development*, 14: 136, 1938. From these published records we selected approximately 100 boys and 100 girls of North European stock, for whom there were records (of chronological age, skeletal age, and height) extending from 6 or 7 years to maturity. It was necessary to include some boys whose epiphyseal closure was not quite complete, extrapolating for probable final stature. Todd Skeletal Ages recorded were evidently two months older than those finally published in Todd's Atlas, and therefore two months were subtracted from each skeletal age, in order to make these records directly comparable to the California material and to the Todd published standards.

†The method and results are described in detail in Bayley, N.: *Skeletal Maturing in Adolescence as a Basis for Determining Percentage of Completed Growth*, *Child Development*, 14: 1, 1943. The Harvard Growth Study data are based on hand x-rays only. Some epiphyses close later than those in either hand or knee, and for this reason there may often be slight growth, usually of the trunk, after these areas are mature. Such growth, however, when it does occur is rarely more than one-fourth inch, which is within the error of measurement.

important that a child be assessed on standards and tables for his or her own sex.) The boys' tables, numbered I, are divided for convenience of handling into two age groups, Table IA for skeletal ages (Sk.A.) below 13 years, and Table IB for those 13 years and above. Two additional tables take care of the younger boys whose skeletal ages deviate widely from their chronological ages. Table IC is for boys accelerated more than one year, if their skeletal ages are $12\frac{1}{2}$ years or less. Table ID is for boys retarded more than one year, if their skeletal ages are $11\frac{3}{4}$ years or less. The girls' tables numbered II are similarly divided: Table IIA for girls with skeletal ages of 11 years or less, and Table IIB for those above 11 years. The supplementary tables for the younger, more deviate girls are: Table IIC for girls who are accelerated more than one year and with skeletal ages of 14 years or less; and Table IID for girls who are retarded more than one year and whose skeletal ages are under 12 years.

Once the correct table is selected the predictions may be read directly from the table. Find the column which represents the child's skeletal age and the line which represents his height. The figure in the square where the two intersect is his predicted mature height. For example, a $10\frac{1}{2}$ -year-old boy who is 57 inches tall and has a bone age of 11 years should be expected, from Table IA, to have a mature height of 70.4 inches. If, however, this boy's chronological age is 8 years, 9 months, he is accelerated more than one year and, according to Table IC, his expected adult height will be 72.0 inches. On the other hand, if he is 13 years, 3 months old, with this same height and skeletal age, we might (if we did not know his skeletal age) expect him to be a very short adult (64.6 inches, Table IB), instead of the more likely 69.3 inches predicted from Table ID.

ILLUSTRATIVE CASES

The close relationship of skeletal maturing to growth in height is illustrated in Tables III and IV and Figs. 1 and 2 for two girls whose skeletal ages are very deviate from their chronological ages. One patient (Case 6F) (Berkeley Growth Study⁵) is very mature for her age, and another (Case 1970) (Harvard Growth Study) is retarded in skeletal maturity. Tables III and IV give, for each of these cases, the age at every measurement with the corresponding skeletal age and height. From these measures we have computed the per cent of her mature height attained at each earlier age: these percentages are used in plotting the individual curves shown in Figs. 1 and 2 in relation to the group norms. The individual curves are presented together with the smoothed curve of the means for the groups from which the tables were constructed. The shaded area represents the percentages included within one standard deviation from the mean, or the middle 67 per cent of the cases.

The per cent of her own mature height achieved by Case 6F is (at most ages) far above the average for children her age (Fig. 1). Predicted height based on chronological age would be greatly overestimated. But when she is compared with children of the same skeletal age (Fig. 2) her curve is much closer to the group average. Case 1970 shows just the opposite trend, being retarded for her chronological age (Fig. 1) but not for her skeletal age (Fig. 2).

TABLE IC. FOR ESTIMATING MATURE HEIGHT OF BOYS ACCELERATED MORE THAN ONE YEAR, BUT WITH SKELETAL AGES UNDER 13 YEARS

Skeletal Age	7-0	7-3	7-6	7-9	8-0	8-3	8-6	8-9	9-0	9-3	9-6	9-9	10-0	10-3	10-6	10-9	11-0	11-3	11-6	11-9	12-0	12-3	12-6
% of Mature Height	67.0	67.6	68.2	68.9	69.4	70.1	71.0	71.9	72.6	73.4	74.1	75.1	75.9	76.8	77.7	78.3	79.2	80.0	80.8	81.5	82.5	83.5	84.5
Ht. (inches)																							
43	64.2	63.6																					
44	65.7	65.1	64.5	63.9																			
45	67.2	66.6	66.0	65.3																			
46	68.7	68.0	67.4	66.8																			
47	70.1	69.5	68.9	68.2	67.7	67.0	66.2	65.4															
48	71.6	71.0	70.4	69.7	69.2	68.5	67.6	66.8	66.1	65.4	64.8												
49	73.1	72.5	71.8	71.1	70.6	69.9	69.0	68.2	67.5	66.8	66.1	65.2	64.6										
50	74.6	74.0	73.3	72.6	72.0	71.3	70.4	69.5	68.9	68.1	67.5	66.6	65.9	65.1	64.4	63.9							
51	76.1	75.4	74.8	74.0	73.5	72.8	71.8	70.9	70.2	69.5	68.8	67.9	67.2	66.4	65.6	65.1	64.4	63.8					
52	77.6	76.9	76.2	75.5	74.9	74.2	73.2	72.3	71.6	70.8	70.2	69.2	68.5	67.7	66.9	66.4	65.7	65.0	64.4	63.8			
53	78.4	77.7	76.9	76.4	75.6	74.6	73.7	73.0	72.2	71.5	70.6	69.8	69.0	68.2	67.7	66.9	66.2	65.0	65.0	64.2	63.5	62.7	
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Note: If deviation in skeletal age is more than two years, estimate is height predicted from this table, "or taller."

TABLE ID. FOR ESTIMATING MATURE HEIGHT OF BOYS RETARDED MORE THAN ONE YEAR BUT WITH SKELETAL AGES UNDER 12

	6-0	6-3	6-6	6-9	7-0	7-3	7-6	7-9	8-0	8-3	8-6	8-9	9-0	9-3	9-6	9-9	10-0	10-3	10-6	10-9	11-0	11-3	11-6	11-9
Skeletal Age	69.5	69.8	70.3	71.0	71.6	72.5	73.0	73.7	74.2	74.9	75.8	76.7	77.4	78.2	78.9	79.7	80.3	81.0	81.2	81.8	82.2	83.0	83.5	84.0
% of Mature Height																								
Ht. (inches)																								
43	61.9	61.6	61.2	60.6	60.0																			
44	63.3	63.0	62.6	62.0	61.4	60.7	60.3																	
45	61.7	61.5	61.0	60.4	62.8	62.1	61.6	61.0																
46	66.2	65.9	65.4	61.8	64.2	63.4	63.0	62.4	62.0	61.4	60.7	60.0												
47	67.6	67.3	66.9	66.2	65.6	61.8	64.4	63.8	63.3	62.8	62.0	61.3												
48	69.1	68.8	68.3	67.6	67.0	66.2	65.8	65.1	64.7	64.1	63.3	62.6	62.0	61.4	60.8	60.2								
49	70.5	70.2	69.7	69.0	68.4	67.6	67.1	66.5	66.0	65.4	64.6	63.9	63.3	62.7	62.1	61.5	62.3	61.7	61.6	61.1				
50	71.9	71.6	71.1	70.4	69.8	69.0	68.5	67.8	67.4	66.8	66.0	65.2	64.6	64.0	63.4	62.7	62.3	61.8	61.2	61.0	63.6	63.3	62.7	62.3
51	73.4	73.1	72.5	71.8	71.2	70.6	70.1	69.4	68.7	68.1	67.3	66.5	65.9	65.2	64.6	64.0	63.5	63.0	62.8	62.3	61.8	61.5	63.9	63.5
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Note: If deviation in skeletal age is more than two years, estimate is height predicted from this table, "or shorter."

TABLE IID. FOR ESTIMATING MATURE HEIGHT OF GIRLS RETARDED MORE THAN ONE YEAR, BUT WITH SKELETAL AGES UNDER 12 YEARS

Skeletal Age	6-0	6-3	6-6	6-9	7-0	7-3	7-6	7-9	8-0	8-3	8-6	8-9	9-0	9-3	9-6	9-9	10-0	10-3	10-6	10-9	11-0	11-3	11-6	11-9
% of Mature Height	74.2	74.5	75.0	75.7	76.5	77.4	78.0	78.7	79.8	80.5	81.3	82.0	82.8	83.8	84.5	85.2	86.1	86.8	87.6	88.0	88.2	89.0	90.0	91.0
Ht. (inches)																								
40	53.9	53.7	53.3	52.8																				
41	55.3	55.0	54.7	54.2																				
42	56.6	56.4	56.0	55.5																				
43	58.0	57.7	57.3	56.8	56.2	55.6	55.1																	
44	59.3	59.1	58.7	58.1	57.5	56.8	56.4	55.9	55.1	54.7	54.1	53.7	53.1	52.5	52.1	51.6	51.1	50.7						
45	60.6	60.4	60.0	59.4	58.8	58.1	57.7	57.2	56.4	55.9	55.4	54.9	54.3	53.7	53.2	52.8	52.3	51.8	51.4	51.1				
46	62.0	61.7	61.3	60.7	60.1	59.4	59.0	58.4	57.6	57.1	56.6	56.1	55.6	54.9	54.4	54.0	53.4	53.0	52.5	52.3	51.7			
47	63.3	63.1	62.7	62.1	61.4	60.7	60.3	59.7	58.9	58.4	57.8	57.3	56.8	56.1	55.6	55.2	54.6	54.1	53.7	53.4	53.3	52.8		
48	64.5	64.4	64.0	63.4	62.7	62.0	61.5	61.0	60.2	59.6	59.0	58.5	58.0	57.3	56.8	56.3	55.7	55.3	54.8	54.5	54.4	53.9	53.3	52.7
49	65.0	65.8	65.3	64.7	64.1	63.3	62.8	62.3	61.4	60.9	60.3	59.8	59.2	58.5	58.0	57.5	56.9	56.5	55.9	55.7	55.6	55.1	54.4	53.9
50	67.4	67.1	66.7	66.1	65.4	64.6	64.1	63.5	62.7	62.1	61.5	61.0	60.4	59.7	59.2	58.7	58.1	57.6	57.1	56.8	56.7	56.2	55.6	54.9
51	67.4	66.7	65.9	65.4	64.8	63.9	63.4	62.7	62.2	61.6	60.9	60.4	59.9	59.2	58.8	58.2	57.8	57.3	56.7	56.0				
52	68.7	68.0	67.2	66.7	66.1	65.2	64.6	64.0	63.4	62.8	62.1	61.5	61.0	60.4	59.9	59.4	59.1	58.8	58.4	57.8	57.1			
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Note: If deviation in skeletal age is more than two years, estimate is height predicted from this table, "or shorter."

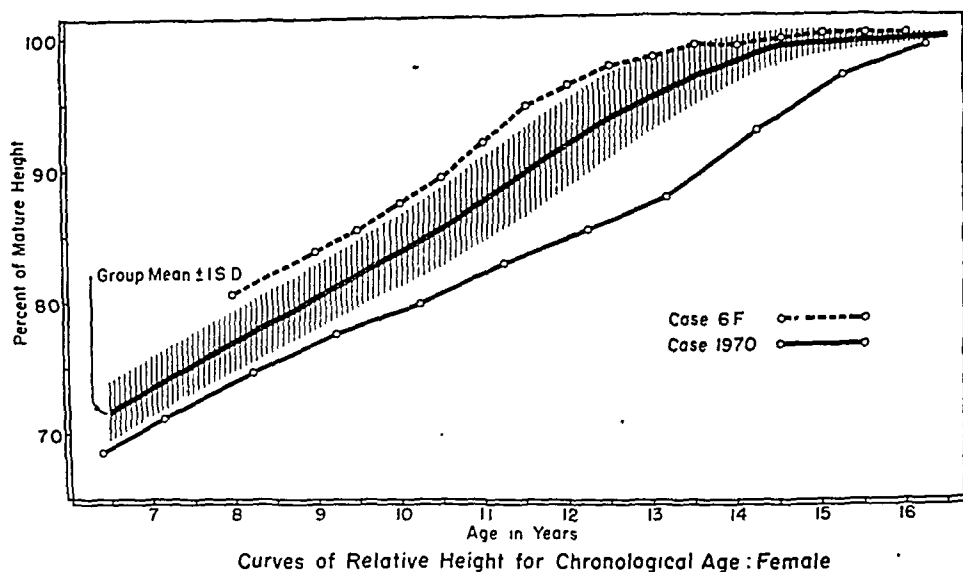


Fig. 1.—Curve of the average per cent of their own mature height achieved, at successive chronological ages, by 100 girls. Shown in comparison are two individual cases, a fast-maturing girl (No. 6F), and a slow-maturing girl (No. 1970).

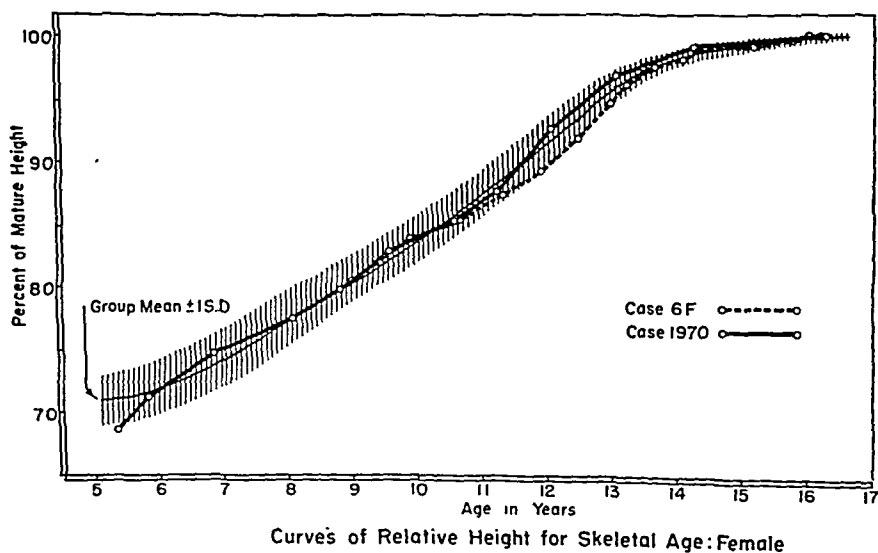


Fig. 2.—Curve of the average per cent of their own mature height achieved, at successive skeletal ages, by 100 girls. Shown also are the curves of the relative heights of the same slow-maturing and fast-maturing girls as shown in Fig. 1 (No. 6F and No. 1970), plotted against their skeletal ages.

ACCURACY OF PREDICTION

The degree of accuracy of prediction is indicated in Tables V and VI. Individual children's heights were predicted in two ways: they were read from the tables on the basis of skeletal age by the method described, and they were also predicted from chronological age alone, using Tables IA and IB and IIA and IIB, as though they were chronological age tables. By computing the differences between actual mature height and these predicted heights, the error of prediction was determined for two groups of children at successive ages. These groups are (1) twenty Berkeley girls⁵ who were not included in the construction of the tables, and (2) the Harvard Growth Study boys (there were no data available on fully mature boys not used in developing the prediction tables;

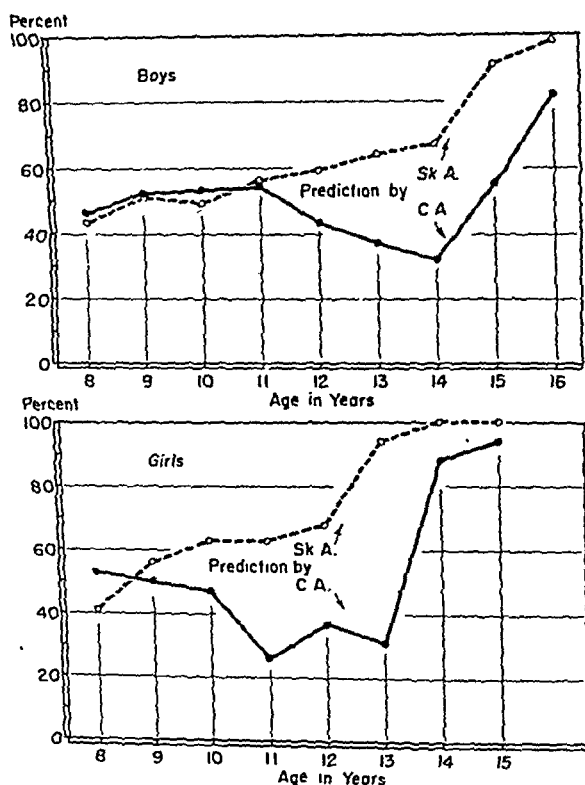


FIG. 3.—The per cent of cases for whom prediction was within one inch of actual final height; A, 100 Massachusetts boys; B, 20 California girls.

ideally it is preferable to test the usefulness of the tables on cases not used in their construction). The average error of prediction is smaller when prediction is made from skeletal ages than when made from chronological ages only. This is shown both by the means of the prediction errors, and by their standard deviations, which show a clustering of predictions much closer to the true height when skeletal age is made the basis of prediction. The relative accuracy of predic-

tion from skeletal age, as compared with chronological age, is shown in another way in Fig. 3, which shows for ages 8 to 16 the per cent of cases for whom the prediction is accurate to an inch or better. Examples of the error of prediction in individual cases are shown for the two deviate girls (Case 6F and Case 1970) in Tables III and IV, respectively. Again we see that the use of skeletal ages greatly increases the accuracy of prediction.*

It must be kept in mind, however, that for the younger ages the error is often as much as an inch or even more. The greatest value to be gained from

TABLE III. A GIRL WHO IS ACCELERATED IN SKELETAL DEVELOPMENT
Case 6F—Mature Height = 65.4 Inches

C.A. YR.-MO.	SK.A. YR.-MO.	HEIGHT (INCHES)	PER CENT MATURE HEIGHT	PREDICTED HEIGHT FROM C.A. (INCHES)	ERROR OF C.A. PREDICTIONS (INCHES)	PREDICTED HEIGHT FROM SK.A. (INCHES)	ERROR OF SK.A. PREDICTIONS (INCHES)
8-0	9-0	52.7	80.6	68.0	+2.5	65.0	-0.4
9-0	9-11	54.9	83.9	67.8	+2.3	65.6	+0.2
9-6	10-8	55.9	85.5	68.0	+2.5	66.4	+1.0
10-0	11-4	57.2	87.5	68.1	+2.6	65.9	+0.5
10-6	11-11	58.5	89.4	68.4	+2.9	65.5	+0.1
11-0	12-6	60.2	92.0	69.0	+3.5	65.6	+0.2
11-6	13-0	62.0	94.8	69.5	+4.0	65.9	+0.5
12-0	13-3	63.0	96.3	68.7	+3.2	66.0	+0.6
12-6	13-8	63.9	97.7	68.3	+2.8	66.1	+0.7
13-0	14-1	64.3	98.3	67.3	+1.8	65.7	+0.3
13-6	14-5	64.9	99.2	66.8	+1.3	65.8	+0.4
14-0	15-2	64.9	99.2	66.2	+0.7	65.5	+0.1
14-6	15-9	65.2	99.7	66.1	+0.6	65.5	+0.1
15-0	16-0	65.4	100.0	66.1	+0.6	65.5	+0.1
15-6	16-2	65.4	100.0	65.8	+0.3	65.5	+0.1
16-0	16-3	65.4	100.0	65.5	+0.1	65.4	+0.0
Mean error = +1.98					Mean error = +0.30		

TABLE IV. A GIRL WHO IS RETARDED IN SKELETAL DEVELOPMENT
Case 1970—Mature Height = 62.2 Inches

C.A. YR.-MO.	SK.A. YR.-MO.	HEIGHT (INCHES)	PER CENT MATURE HEIGHT	PREDICTED HEIGHT FROM C.A. (INCHES)	ERROR OF C.A. PREDICTIONS (INCHES)	PREDICTED HEIGHT FROM SK.A. (INCHES)	ERROR OF SK.A. PREDICTIONS (INCHES)
6-5	5-4	42.6	68.6	58.6	-3.6	59.6	-2.6
7-2	5-10	44.3	71.2	59.3	-2.9	60.0	-2.2
8-3	6-10	46.5	74.7	59.4	-2.8	61.2	-1.0
9-3	8-1	48.2	77.6	60.1	-2.1	60.2	-2.0
10-3	8-10	49.7	79.9	58.5	-3.7	60.4	-1.8
11-3	9-7	51.6	82.9	58.7	-3.5	61.0	-1.2
12-3	10-7	53.1	85.4	57.3	-4.9	60.5	-1.7
13-2	11-3	54.5	87.8	56.6	-5.6	61.3	-0.9
14-3	12-1	57.7	92.8	58.6	-3.6	62.7	+0.5
15-3	13-1	60.2	96.9	60.7	-1.5	62.9	+0.7
16-3	14-3	61.7	99.2	61.8	-0.4	62.6	+0.4
17-3	16-3	62.2	100.0	62.2	0.0	62.3	+0.1
Mean Error = -2.88					Mean Error = -0.98		

*Skeletal Ages for the Berkeley Growth Study cases are averages of hand and knee assessments, while the Harvard Growth Study skeletal ages were read from x-rays of a part of the hand only. This may account for the greater accuracy of prediction from skeletal age of Case 6F as compared with Case 1970, as well as for the Berkeley girls as compared with the Harvard boys (Tables V and VI).

TABLE V. ERROR IN HEIGHT PREDICTION BY CHRONOLOGICAL AGE AND SKELETAL AGE—
BERKELEY GROWTH STUDY (GIRLS)

AGE IN YEARS AND MONTHS	PREDICTION BY C.A.			PREDICTION BY S.K.A.	
	N	MEAN ERROR (INCHES)	S.D.	MEAN ERROR (INCHES)	S.D.
8-0	17	+ .15	1.55	-.76	1.44
9-0	18	+ .05	1.57	-.09	1.64
9-6	18	+ .71	1.74	+1.13	1.50
10-0	19	+ .67	1.85	-.34	1.29
10-6	19	+ .93	2.09	-.62	1.01
11-0	19	+1.06	2.05	-.69	.88
11-6	19	+1.30	2.35	-.61	1.02
12-0	19	+1.01	2.20	-.27	.94
12-6	19	+ .88	1.89	-.23	.60
13-0	16	+ .44	1.54	-.03	.55
13-6	16	+ .06	1.30	+0.08	.38
14-0	17	+ .26	.93	+0.21	.36
14-6	17	+ .21	.67	+0.09	.32
15-0	17	+ .29	.49	+0.11	.18
15-6	19	+ .21	.33	+0.05	.11
16-0	17	- .06	.24	-.05	.15

TABLE VI. ERROR IN HEIGHT PREDICTION BY CHRONOLOGICAL AGE AND SKELETAL AGE—
HARVARD GROWTH STUDY (BOYS)

AGE IN YEARS AND MONTHS (MIDPOINT)	PREDICTION BY C.A.			PREDICTION BY S.K.A.		
	N	MEAN ERROR (INCHES)	S.D.	N	MEAN ERROR (INCHES)	S.D.
7-6	102	-.61	1.76	96	-.23	1.73
8-6	97	+0.07	1.65	96	+0.21	1.60
9-6	103	-.004	1.66	103	+0.30	1.48
10-6	98	-.04	1.64	97	+0.21	1.39
11-6	102	+0.08	1.94	98	+0.04	1.35
12-6	100	+0.49	2.59	97	+0.07	1.26
13-6	102	+0.46	2.85	100	+0.20	1.11
14-6	99	+0.33	2.38	96	-.32	1.00
15-6	98	+0.31	1.45	97	-.28	.60
16-6	96	+0.35	.69	96	+0.20	.39
17-6	91	+0.27	.31	91	+0.10	.22

the skeletal age tables is for the period during which adolescent growth spurts occur—that is, after 10 years for girls, and 12 years for boys.

DISCUSSION

Two other recent studies, besides the one on which this report is based, have reported similar relationships between growth in size and developmental changes in the skeleton. Simmons,⁶ working on the Brush Foundation material from which the Todd standards were developed, reports findings closely similar to those found for the children in the California Adolescent Growth Study.¹ Simmons' data as well as ours show that skeletal age is much more highly correlated with relative size than is chronological age. She also calls attention to the possibility of predicting adult height on the basis of skeletal age. But she does not give specific methods for computing the predictions.

Gill and Abbott⁷ have devised a method for predicting height, in order to predict growth of the femur and tibia. Their purpose is a practical one—to de-

termine the amount of change to make in osteotomy for equalizing leg lengths. They use published data on percentile groups of heights at successive ages, and predict from skeletal age, disregarding chronological age, if a child is retarded or accelerated more than six months in skeletal age. Our method appears to be more accurate than theirs because of refinements made possible by the nature of the data available to us. It should prove of value for the same purposes.

Shuttleworth⁸ has developed tables for predicting mature height, using other criteria of physical maturity, primarily the age at maximum growth. His main tables, for prediction from a given initial height and age, are intended for children maturing at the average rate. To correct for deviations in velocities of maturing he gives a series of supplementary tables which can be used only if a child has been measured at least twice with *exactly* one year intervening between measurements. The prediction is then determined from height, age, and the annual increment in stature since the previous measure. This procedure is very cumbersome and requires an exactitude of measures and intervals which are rarely available clinically. However, when correctly determined (and when increments can be correctly located in relation to age at maximum growth) predictions may yield results similar to ours, because both systems have grown out of similar premises concerning characteristic growth trends of children with differing velocities of physical maturing.

It is hoped that the tables presented here will have clinical usefulness. They should prove of value, when used with x-rays of the hand and/or other ossification centers which have been assigned skeletal ages, in predicting the adult height of children whose growth is incomplete. It seems very likely that further knowledge of the factors influencing growth will eventually make it possible to predict height with even greater accuracy than the use of skeletal-age-height tables permit.

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THE USE OF PROSTIGMINE IN THE MANAGEMENT OF INFANTILE CEREBRAL PARALYSIS

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IN SPITE of much study and innumerable special investigation as to the causative factors and pathology of infantile cerebral paralysis (variously known as spastic paralysis, Little's disease, or cerebral diplegia), at present there is little unanimity of opinion. Even less agreement exists as to the preferred method of treatment.

The most widely prevalent theory as to the etiology of this condition is that it is necessarily caused by birth trauma or obstetric mismanagement. Recently, however, Heyman¹ reviewed the literature on this subject and came to the conclusion that there are many factors which give rise to the clinical entity known as spastic paralysis. Among these he listed neuropathic heredity, primary degeneration of the brain or developmental arrest, infections, premature birth, hemorrhagic disease of the newborn, asphyxia, and anoxemia.

The traumatic factor, whether or not it is the most important one, has in any case received the most attention. It is commonly believed that a difficult and prolonged labor or an instrumental or breech delivery may result in intracranial hemorrhage. Such bleeding is due to a laceration of the dura mater or possibly in the brain substance itself. In some instances the lesion may be more widespread as a result of a temporary obstruction of the circulation. Degeneration of the nervous tissue followed by sclerosis may result in foci of atrophy and softening. Similar changes can and do occur in the spinal cord, especially when there has been traction on the neck during delivery.

The clinical classification is as difficult as the etiologic and pathologic.² The spastic diplegias are usually not manifest for the first few months of life. However, there may be some early spasticity or the infant's limbs may be closely adducted. These signs become more evident as the child learns to walk, a function which is often delayed till the age of 2, 3, or even 4 years. The gait is usually spastic and commonly known as "scissors gait." If the lesion is confined to the upper motor cortex, the spastic paralysis is limited to the lower extremities.

Even in the mildest cases there is definite evidence of involvement of the pyramidal tract in the form of increased deep tendon reflexes. It follows that there is considerable muscular weakness or even paralysis. No sensory disturbances are usually seen.

Other signs of cerebral involvement are generally present. Various grades of mental impairment are common, ranging from irritability and hyperexcitability to imbecility or idiocy.² True epileptic convulsions are suffered by some patients. The speech is likely to be impaired, perhaps due to spasticity of the muscles used in articulation. It is believed that not infrequently the mental retardation may be due at least in part to discouragement of education of the

child because of his physical impairment. In this respect a very careful history is essential. Painsstaking observation over a period of several months may often determine whether or not the condition is progressive, and whether or not there is true mental retardation.

TREATMENT

The treatment of infantile cerebral paralysis has been considered highly unsatisfactory. The essential principle involved is one of training and rehabilitation over a prolonged period. Some clinicians advocate operative intervention as an adjunct to the re-education program. For example, the Foerster operation of cutting certain sensory roots to overcome the spasticity has been reported to have produced good results in some cases. A similar procedure on the motor nerves (Stoffel operation) is designed to bring about the same effect. However, all such operative procedures have the disadvantage of permanently interrupting nerve pathways and of inducing physiologic changes which are undesirable.

More hope can be expected from physiotherapeutic measures such as massage, baking, active and passive motion, and coordinating exercises. Persistent re-educational measures are the sheet anchor of therapy. Recently a drug has been added to our therapeutic armamentarium which aids materially by decreasing or abolishing muscle spasticity, thus helping the patient to relax sufficiently to allow slow, controlled movement of the extremities. The drug chosen is prostigmine.

Prostigmine is a parasympathetic stimulant which has recently been shown to have a depressant action on the spinal cord. Deep reflexes can be abolished and muscle spasticity appreciably lessened by the administration of prostigmine in man.³⁻⁷

Accordingly, in 1943, we began to use prostigmine bromide by mouth in an attempt to reduce the muscle spasticity in our patients. Cases at first were chosen at random, regardless of age or chronicity. However, it was soon discovered that the younger the patient was at the beginning of therapy, the more likely was prostigmine to afford beneficial results. Since starting this work Kabat⁸ as well as Schaubel⁹ have reported very favorable results in similar cases with prostigmine therapy.

The dosage was governed by the age of the patient, but the minimum dose in all cases regardless of age was 5 mg. of prostigmine bromide (one-third of a standard 15 mg. tablet). When first administered the patient was instructed to take the minimum dose (5 mg.) by mouth three times per day. After a period of two weeks, provided no adverse reaction was observed, the dose was given four or more times per day. Strangely enough, single doses larger than 5 mg. proved less beneficial and more likely to cause diarrhea and abdominal cramps, especially in small children.

It was found in the cases observed and treated that in children under the age of 12 years there was a definite lessening of spasticity and an increase in the function of the muscles involved. Results were often noted as early as 2

or 3 weeks after the beginning of treatment. However, it was quite evident that prostigmine medication must be continued for at least six months, or until further improvement was no longer noted. It was found that if the drug was discontinued at the end of two or three months there was a partial recurrence of the former spastic symptoms. On the contrary, if medication was continued regularly and persistently (from four to eight times daily) for six months there seemed to develop an habitual improvement even after treatment was discontinued. As a matter of fact, during this period the patient apparently "learned" how to relax.

No such beneficial results were observed in the two adult cases so treated (aged 32 and 34, respectively). Although prostigmine appeared to afford some relaxation, there was not sufficient depression of the spasticity to enable the patient to relax voluntarily in order to respond to muscle re-education and training.

To date, some twenty-five patients have been subjected to prostigmine therapy, the great majority of them being between the ages of 2 and 6 years. In general the results have been most encouraging. It is to be emphasized that the usually accepted, standard forms of therapy, including physiotherapeutic measures and re-education must be employed concomitantly with prostigmine medication if the most favorable results are to be obtained. Such measures usually can be efficiently carried out by the child's mother and the patient's general condition and progress checked by the attending physician every two weeks. Furthermore, it is believed that frequent small doses of prostigmine bromide by mouth, administered throughout the waking hours, afford a more continuous decrease of muscle spasm than do larger doses given less often.

SUMMARY

Although it must be acknowledged that this is a small series of cases upon which to base any definite conclusion, it is thought that there is sufficient evidence to warrant the continued use of prostigmine as suggested and eventually to be able to compile end results from numerous investigators and draw conclusions that may be standardized, thereby obtaining some benefit for a condition that up to now has been most discouraging to both patient and physician. This preliminary report is published in the hope of stimulating further study and research in the adjunctive use of prostigmine in the management of children with infantile cerebral paralysis.

REPRESENTATIVE CASE REPORTS

CASE 1.—J. B., a 2½-year-old white boy, was first seen in the clinic on Nov. 11, 1942. The father gave a history that the child had had symptoms of a spastic cerebral paralysis since birth, and that the only previous therapy had been the use of special corrective shoes.

Examination revealed marked spasticity of the right upper extremity. The right Achilles tendon was quite taut, and only when the child's attention was distracted could the foot be brought into a neutral position. The upper extremity was almost functionless.

The parents were given instructions as to massage and exercises of the right upper extremity. In addition the right Achilles tendon was lengthened by surgery.

He was seen in February, 1943, at which time walking was quite satisfactory although the right Achilles tendon still was quite taut. In June, 1943, a splint was applied to the left hand in order to hold the thumb and other fingers in the extended position.

Prostigmine therapy was instituted in Sept., 1943, 4 mg. (prepared in capsule form) being given three times per day. Gradual, increasing improvement was noted during the next seven months during which time the prostigmine was increased to 5 mg. given six times per day. When last seen in October, 1944, the child could walk quite well, could throw a ball, and was generally improved to a considerable degree. (Prostigmine therapy had been started again in July, 1944).

CASE 2.—T. T., a 2½-year-old white boy, was first seen by us in October, 1944. Although the chief complaint was flat feet, examination revealed sufficient spasticity of the left lower extremity to justify a diagnosis of spastic cerebral paralysis.

Treatment at first consisted only of the wearing of special corrective shoes having "pigeon toe" wedges. When seen one month later, at which time the spasticity was pronounced, 5 mg. of prostigmine bromide was prescribed three times per day and coordinating exercises were demonstrated. Three weeks later there was an appreciable decrease in spasticity of the left lower extremity. Prostigmine dosage was gradually increased until 30 mg. daily was given in divided doses. When last seen in March, 1945, (four months after the initiation of prostigmine therapy) the child was greatly improved, and walking was almost normal.

Most of the other cases follow a similar pattern and have for this reason not been recorded.

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CORD TRANSFUSIONS IN NEWBORN INFANTS

A REPORT OF NINETY-NINE CORD TRANSFUSIONS IN PREMATURE BABIES,
TWENTY-ONE IN FULL-TERM BABIES AND SEVENTY-EIGHT
IN BABIES OF RH-NEGATIVE MOTHERS

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FOLLOWING a long labor, difficult forceps delivery, or breech extraction, the infants are frequently in severe shock. Not infrequently they are suffering from hemorrhage, which may not always be apparent at birth but develops shortly after. In premature babies the blood has a low content of vitamin K and prothrombin, and premature infants are much more subject to hemorrhage and will not withstand as much trauma as full-term infants. Taking these facts into consideration, it would seem that if newborn full-term infants following a difficult labor and all premature infants were given some adult blood immediately following birth, such a transfusion might overcome shock, supply the needed vitamin K and prothrombin, as well as furnish nourishment and fully developed red corpuscles to be utilized in carrying on the circulatory functions. The effectiveness of blood transfusions promptly given to combat shock and hemorrhage in battle injuries has been proved beyond a doubt.

Our experience in transfusing thirty-four newborn infants by way of the umbilical vein, with mother's blood as the adult blood provided, was reported in 1944¹; subsequent use of cord transfusions with mother's blood is reported here.

Another hazard to the newborn infant is erythroblastosis. It has been supposed that the Rh factor is involved in the development of this disease, and that one in thirty to fifty of the infants of Rh-negative mothers may be expected to develop it. It would seem that the Rh factor alone does not determine or is not alone present in the development of the disease. Even more prognostic of its occurrence, particularly when found in infants of Rh-negative mothers, is a high count of normoblasts in the cord blood immediately or soon after birth.

Since cord transfusions have proved of value in combating shock and hemorrhage in premature infants and in full-term babies after a hard labor, their value would seem likely in actual or prophylactic treatment of erythroblastosis, a blood dyscrasia, the probable development of which can be expected to some extent among Rh-negative mothers, particularly multipara, and to a larger extent among infants whose cord smears show a high count of normoblasts. Cord transfusions in seventy-eight infants of Rh-negative mothers are reported, together with a discussion of 601 cord smears.

The technique of cord transfusion is also described.

From the Obstetrical Department of the Methodist Hospital.
This study aided by a grant from the Lindridge Research Fund.

TECHNIQUE OF CORD TRANSFUSION

The technique of giving mother's blood to newborn infants by way of the umbilical vein is not difficult, and relatively few conditions make such transfusion impossible.

Mother's blood is preferred because at the time of delivery it contains more prothrombin and vitamin K than the average individual's, the vitamin K having been reinforced by administration during labor. If mother's blood is used only once, as is usually the case, it is not necessary to match the blood before giving the cord transfusion. Even if incompatible and though there may be some reaction, this one transfusion will assist the baby, since the blood will remain in the circulation long enough to exert its beneficial effect. The reason for this is the absence of agglutinins in the baby's blood at birth other than those derived from the mother.

The blood should be withdrawn before the birth under sterile precautions and placed on the delivery table. A 50 c.c. syringe is used containing sufficient citrate to insure against clotting in the syringe; 5 c.c. of a 2 per cent solution of sodium citrate is enough for 35 c.c. of blood. If more than 35 c.c. are withdrawn there is danger of the blood's clotting and clogging the needle, thus making the transfusion impossible without straining the blood. If 50 c.c. of blood are to be used, then 7 or 8 c.c. of the citrate are advisable. When the citrate is first drawn into the syringe, the entire length of the barrel should be moistened with it by withdrawing the plunger of the syringe and allowing the solution to come in contact with the entire inside of the barrel. This seems like a needless precaution, but when a large syringe is used, considerable pressure is needed to force the blood into the umbilical vein, and if the blood comes in contact with the barrel and plunger before being citrated, the plunger is very likely to stick and make the transfusion either very difficult or impossible. If the blood has not been withdrawn before delivery and a transfusion is deemed necessary, then, if the syringe is easily available, it is often possible to draw the blood after the baby is born and give the cord transfusion. This has been done frequently with complete success.

The amount of blood given depends upon the size of the baby and the reason for its use. In giving 500 c.c. of blood to a woman weighing 125 pounds, we give 4 c.c. per pound of body weight. The correct amount for a baby is about 10 c.c. per pound of body weight. A good many of our early transfusions were insufficient, and in several cases the baby's life may have been lost as a result. An insufficient amount was especially likely to be given twins, the amount of blood withdrawn being about enough for one baby; instead of giving it all to one twin, the amount was divided, with neither receiving an adequate amount. We recently delivered twins, each weighing over 6 pounds. We had two syringes with 35 c.c. of blood available. Following the cord transfusion, their progress was excellent.

It is preferable to inject the blood before separating the baby from the mother. The baby is placed on the mother's abdomen or is held with the head

down by an assistant. The cord is clamped and the blood injected into the umbilical vein. The cord should be steadied with the left hand, the barrel of the syringe grasped with the right, and the blood injected by making pressure on the plunger with the chest.

Great care should be taken after entering the cord vein. Should the point of the needle perforate the thin-walled vein, the blood will be injected into the substance of the cord, and a diffuse localized area of hemorrhage will appear. If this happens, the transfusion may be attempted again at a point nearer the baby's body, provided the first attempt was made far enough away from the naval. It is important to select the first site at a maximum distance, usually about twelve inches, to allow for subsequent trials. We have recently found a large, short-bevel, Fordyce needle obviates danger of vein injury.

Delay may make transfusion by the cord route impossible. The blood may enter the vein, the vein distending as far as the umbilicus, but will fail to enter the baby's body.

At times it is advisable to separate the baby from the mother before doing the transfusion. On cutting the cord it is likely to collapse and the veins are hard to identify. If the cord is milked toward the clamp, enough blood can be collected to identify the vein.

The giving of blood seems to have no ill effect on the baby. Frequently the respirations are stimulated, and the baby, previously pale, becomes pink.

CORD TRANSFUSIONS

The first cord transfusion at the Methodist Hospital was given in 1940 to a premature infant (Case 4). The first published report on cord transfusions was in 1944,¹ when thirty-four cases were presented, eighteen in premature infants weighing less than 5½ pounds and sixteen infants weighing over 5½ pounds. There were four deaths, all under thirty-seven weeks' gestation. During 1944 there were 189 cord transfusions with 174 living babies. Ninety-nine cord transfusions were done in premature infants; twenty-one in full-term infants following difficult labor or delivery and seventy-eight in infants of Rh-

TABLE I. TOTAL CORD TRANSFUSIONS, 1940 THROUGH MARCH 1945

	PREMA- TURE INFANTS (37 WK. OR UNDER)	FULL- TERM	MOTHERS Rh-	TOTAL	DEATHS			
					PREMA- TURE INFANTS (37 WK. OR UNDER)	FULL- TERM	MOTHERS Rh-	TOTAL
1940 through								
1943	18	16	-	34	4	-	-	4
1944	99	21	78*	189	15	-	2*	15
Jan, Feb., and March, 1945	22	4	32	58	1	-	-	1
Total	139	41	110	281	20	-	2	20

*Nine of the babies with mothers Rh- were premature infants and have been included in this group as well. Total count of cord transfusions does not include these duplications.

negative mothers. Nine of the last group were also premature infants and reported in that group; thus the total of cord transfusions is nine less than the sum of the three groups. Through March, 1945, fifty-eight cord transfusions have been done.

CORD TRANSFUSIONS IN PREMATURE INFANTS

In 1944, cord transfusions were given to ninety-nine infants of thirty-seven weeks' gestation or under. Of these, fifty-five weighed $5\frac{1}{2}$ pounds or under and forty-four more than $5\frac{1}{2}$ pounds (Table II).

Of the fifty-five in the first weight group, i.e., those weighing $5\frac{1}{2}$ pounds or less, twelve babies weighing between 5 and $5\frac{1}{2}$ pounds all lived; twenty-six weighing from 4 to 5 pounds, and of these three died; of eleven weighing between 3 and 4 pounds, and of these five died. Mortality was 100 per cent in the group weighing 3 pounds and less; two weighing from 2 to 3 pounds, four weighing from 1 to 2 pounds. The total number of deaths was fourteen and nine of these occurred in infants of less than seven months' gestation; only two weighed over 4 pounds; one was a twin who lived for fifteen days and the other, who weighed 4 pounds, 15 ounces, was of thirty-three weeks' gestation, and was delivered following a severe pyelitis of his mother. He received 35 c.c. of his mother's blood by cord transfusion and died in fourteen hours. The mother was Rh positive.

Of the forty-four in the second group, i.e., those weighing over $5\frac{1}{2}$ pounds, there was one stillbirth. The blood had been drawn from the mother thinking the baby would be born alive; the cord transfusion was given with no difficulty. The mother was a diabetic patient.

Weight is apparently not always a true index of ability to survive. An infant who might have weighed 10 or 11 pounds at 9 months, though born prematurely at 7 months and weighing 6 pounds, is, nevertheless, premature.

CORD TRANSFUSION FOLLOWING DIFFICULT DELIVERY

The greatest danger to the infant following a long labor or difficult delivery is cerebral hemorrhage. If this danger could be met, we might not be so anxious to do cesarean sections when the baby seems a little large or the cervix does not dilate as easily as we imagine it should.

TABLE II. CORD TRANSFUSIONS IN PREMATURE INFANTS IN 1944

	BIRTHS	DEATHS	PER CENT
37 weeks and under	99	14	14.1
Over $5\frac{1}{2}$ pounds			
Live births	43	—	0.0
Stillbirths	1	—	—
$5\frac{1}{2}$ pounds or under			
Live births	55	14	25.4
$5\frac{1}{2}$ pounds or under	55	14	25.5
5 to $5\frac{1}{2}$ pounds	12	0	0.0
4 to 5 pounds	26	3	11.5
3 to 4 pounds	11	5	45.4
2 to 3 pounds	2	2	100.0
1 to 2 pounds	4	4	100.0

During 1944, twenty-one cord transfusions were given following difficult deliveries. Twelve were posterior positions, eleven were delivered by medium forceps and thirteen were rotated either by forceps or manually. Eleven of the babies weighed over 8 pounds. In many of these cases the baby's condition was poor, but there were no deaths.

In the 1943 report, sixteen full-term infants were given cord transfusions on similar indications, with no deaths.

CORD TRANSFUSIONS IN BABIES OF RH-NEGATIVE MOTHERS

After the successful use for a number of years of cord transfusions in premature babies and in full-term infants threatened with hemorrhage after a difficult labor, it was thought the method might save some of the babies born of Rh-negative mothers who were affected by the Rh factor. There has been much discussion in both general and scientific magazines about probable death from erythroblastosis of infants of Rh-negative mothers.

Under a grant from the Lindridge Fund, grouping and typing of the blood of maternity patients was begun; at present such tests are done on all ward patients and many private patients. The technique is simple. At the hospital, when taking blood for the blood count of ward patients, the technician expresses several more drops, collecting them in a tube containing 5 c.c. of normal saline. In the doctor's office, when the blood is drawn for the Wassermann, before removing the needle from the syringe, a few drops are forced into the saline bottle; then the needle is removed and the remainder of the blood used for the Wassermann. At the present time, we are drawing enough blood when the Wassermann is taken so that 3 or 5 c.c. of whole blood is sent to the laboratory for grouping and the Rh factor. With both ward and private patients, after the blood is grouped and typed, the report is given the physician on the detachable part of a label he originally filled out. A card stating blood group and Rh factor is also given the patient, somewhat like the "dog tag" given servicemen (Figs. 1 and 2).

During 1944, 1,910 blood specimens were examined; 296, or 15.2 per cent, were Rh negative, and 137 of these patients were delivered in 1944. Two, or 3 per cent, of the babies of these women could be expected to develop some form of erythroblastosis; if the mother was a multipara, probability was more certain. Practically nothing has been suggested to be given the mother as a prophylactic against the disease in her child. The usual treatment of the child, once the disease is manifest, is transfusion with blood of an Rh-negative donor. The disease is sometimes unrecognizable at birth, and one is not looking for it unless the mother is known to be Rh-negative. If the vernix is yellow or the liquor amnii is stained yellow, erythroblastosis should be suspected and a cord smear or blood count made immediately. Even these may be normal and the baby still develop erythroblastosis.

Of the babies of the 137 Rh-negative mothers, seventy-eight were given cord transfusions using mother's blood, and fifty-nine were not. According to Levine² cases for transfusion should be selected on the basis of increasing degree of immunization, i.e., agglutinins with blocking antibodies. There were eight cases

of erythroblastosis or some blood dyscrasia diagnosed as erythroblastosis, three in the transfused group, five in the group not transfused. The three infants in the transfused group recovered; there were, in addition, two deaths, both among premature infants, in which diagnosis of erythroblastosis was not made. In the group not transfused, two of the five died, three recovered.

7A-171	No. _____	OBSTETRICAL RESEARCH NAME No.
PATIENT'S NAME _____		
ADDRESS _____		
PATIENT OF _____		
TYPE _____		
RH _____		
REMARKS: _____		
DATE _____		

Fig. 1.—This is a reproduction of a gummed label with detachable strip which is distributed to the doctors, filled out by them, attached to the blood specimen, and sent to the laboratory. Blood type and Rh factor are filled in and the label along with the patient's card, is returned to the doctor.

7A-153	
METHODIST HOSPITAL	
6th St. & 7th Ave., Brooklyn, N. Y.	
Name _____	
Date _____	
Blood Type _____ Rh _____	
Keep this card. It will be very important to know your blood type if you need a transfusion or wish to give blood for a transfusion.	

Fig. 2.—Reproduction of patient's card.

The two deaths in the transfused group have been included in the report on premature infants. One was the infant weighing 4 pounds, 15 ounces, gestation thirty-four weeks, delivered by cesarean section. Fifty cubic centimeters mother's blood were given by cord transfusion, the baby dying within fourteen hours. The Rh-negative mother had lost one baby at seven and one-half months and had also had a six months' stillbirth. The second premature baby who died weighed 3 pounds, 9 ounces, and was of thirty-one weeks' gestation; he was in critical condition at birth and lived only one hour, ten minutes. The Rh-negative mother was a gravida i, blood group O. The baby was Rh positive, blood group B. Cord smear showed 46 normoblasts. At autopsy internal hydrocephalus was found.

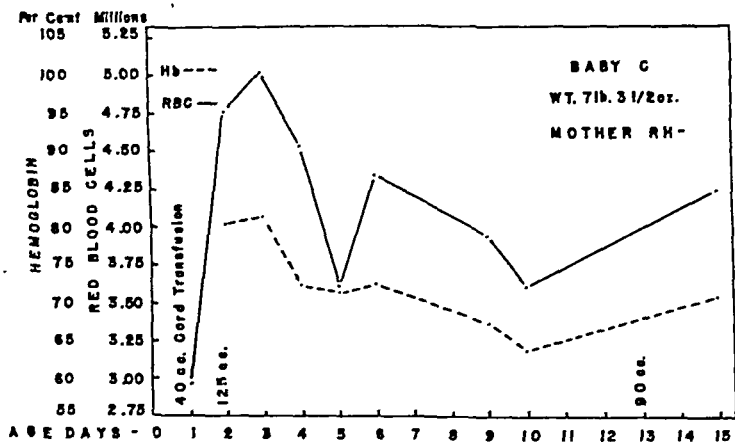


Fig. 3.—Erythroblastosis fetalis, Baby C.

One of the babies in this transfused group who developed erythroblastosis and recovered was a full-term male child weighing 7 pounds, 31½ ounces. He had received 40 c.c. mother's blood by cord transfusion. The mother, who had had one normal child and lost a premature infant of six months' gestation, who had lived three days, was Rh negative; the father and baby, Rh positive. Condition was fair at birth, but the skin soon became yellow and the spleen was palpable one fingerbreadth below the costal margin. The first blood count had showed 2,900,000 red cells with marked change in size and shape of the cells but no normoblasts. On the day after delivery, the baby was given 125 c.c. of blood from a professional Rh-negative donor. The count increased to 4,760,000 with 25 nucleated red cells per 100 white cells. Two days later the red cells were 5,050,000 with 6 nucleated red cells. At 9 days of age the count had dropped to 3,600,000, and at 42 days to 2,830,000. The baby made an excellent recovery. (Baby C, Fig. 3.)

Two others of the transfused group were thought to have some blood dyscrasia, diagnosed as erythroblastosis. Normoblast count was above 15. Both recovered.

In the group not given cord transfusions, there were five cases of erythroblastosis with two deaths. The first of the two infants who died was full term, condition good at birth. The mother was Rh negative; the father and baby, Rh positive. The mother had had a normal baby in 1941; she had had a hemorrhage following delivery and was transfused. At the age of 28, June 20, 1944, she was delivered of her second child. The baby nursed well until the third day, when he became very jaundiced; the liver was palpable one fingerbreadth below the costal margin. The blood count was 4,860,000, with no normoblasts. The baby was given 25 c.c. of blood from an Rh-negative donor but died the following day. Autopsy showed hematopoiesis in the liver.

The second baby in the nontransfused group who died was delivered by cesarean section Dec. 12, 1944. The mother had had one normal child by cesarean section, was 28 years old, and Rh negative. The baby weighed 6 pounds, 15 ounces, and seemed in good condition at birth. Red cell count, however, was 4,970,000, with 142 normoblasts. Nine hours after birth, the baby was given 105 c.c. of blood from an Rh-negative donor of the same blood type. The following day the red cell count was 5,230,000 and the normoblasts 158 per 100 white cells. The skin became yellow and the spleen palpable. The condition soon became critical. Coffee-ground vomitus and blood were coming from the nose and mouth, and the baby died on the second day.

Three other infants with a count of more than 15 normoblasts, in whom a diagnosis of erythroblastosis was made, received early intravenous transfusions and lived.

The history of the seventy-eight Rh-negative mothers whose babies were given cord transfusions of mother's blood showed that forty-one were multiparas; thirty-four of these multiparas had previously had full-term pregnancies, four premature babies, ten miscarriages, three stillbirths, and with four the babies had died. Thirty-seven were primiparas. (Table III.)

TABLE III. PARITY IN 137 MOTHERS RH-

	CORD TRANSFUSION		
	YES	NO	TOTAL
Gravida 1	37	25	62
Gravida 2	23	21	44
Gravida 3	12	8	20
Gravida 4	3	3	6
Gravida 5	3	2	5
Total	78	59	137

Thirty of the seventy-eight patients were apparently over term when delivered; ten, forty-two weeks, and twenty, forty-one weeks. Twenty-three were delivered at term, forty weeks. There were nine under thirty-seven weeks, including the two whose babies died, already reported. (Table IV, A.)

Six of the fathers in this group were Rh negative; in the group not transfused eleven were Rh negative. A comprehensive test of father's blood was not made, however, many of the fathers being in service, or for some other reason their blood not being available for testing. In the transfused group, nineteen

TABLE IV, A AND B. SEVENTY-EIGHT CORD TRANSFUSIONS; MOTHERS RH-

A. GESTATION		B. AMOUNT OF BLOOD TRANSFUSED	
42 weeks	10	?	7
41 weeks	20	10 c.c.	2
40 weeks	23	15 c.c.	1
39 weeks	10	20 to 25 c.c.	5
38 weeks	5	30 c.c.	7
37 weeks	1	35 c.c.	9
Under 37 weeks	9	40 to 45 c.c.	30
		50 c.c.	17
Total	78	Total	78

TABLE V. RH FACTOR IN 137 BIRTHS

	CORD TRANSFUSIONS		
	YES	NO	TOTAL
Mother Rh-	78	59	137
Father Rh-	6	11	17
Father Rh+	41	11	52
Father not tested	31	37	68
Baby Rh-	19	5	24
Baby Rh+	42	12	54
Baby not tested	17	42	59

babies of sixty-one tested were Rh negative, and forty-two, Rh positive; five in the nontransfused group were Rh negative, and twelve, Rh positive among seventeen tested (Table V).

The amount of mother's blood given in the cord transfusion varied from 10 c.c. to 50 c.c. Thirty received from 40 to 45 c.c., and seventeen, 50 c.c. (Table IV, B). In the case of the very small amounts, the transfusion was unsuccessful and an adequate amount of blood could not be given. However, if any blood at all was given by the cord route, the case was counted as a cord transfusion.

Administration of blood via cord transfusion at birth from an Rh-negative mother to her baby as an aid in the treatment of erythroblastosis is contrary to the generally accepted rule of using Rh-negative donor's blood. The infant who received a cord transfusion, in whom erythroblastosis developed (Baby C), had no normoblasts in the blood following the cord transfusion, though jaundice was marked. Twenty-five normoblasts were found the second day. It may be argued that the jaundice in this case was caused by reaction to the mother's blood. If this is so, why did not a similar reaction occur in the other cases similarly transfused?

Three interesting cases seen in 1945 and one in 1944 are discussed immediately following. In the first, the baby was transfused the second day with 90 c.c. of mother's blood; later it was discovered the mother was Rh negative, her blood having an exceptionally high agglutinin titer. There was no reaction. The second is a case of jaundice in a cord-transfused infant of an Rh-negative mother, with recovery; the third, a case of jaundice in an infant of an Rh-negative mother, not cord-transfused, with recovery. The fourth reports death of three of five infants, both parents Rh positive.

CASE HISTORIES

CASE 1.—Observed this year. The mother had had a normal baby by her first husband seven years before. When she was delivered in 1945, it was thought she was Rh positive. The baby was not given a cord transfusion. He very soon became extremely jaundiced and was thought to have an obstruction of the bile ducts. He was given 90 c.c. of his mother's blood on the second day and showed much improvement. The blood count was normal until the eighth day, when it was found to have dropped to 4,200,000 with a hemoglobin of 80 per cent. When the baby was 14 days old, the red cells were 2,700,000 and the hemoglobin 60 per cent. He was given 90 c.c. of blood from a professional Rh-negative donor. The blood of the mother was tested by Dr. Levine, who found the agglutinins of a titer of 1:80. It is rather hard to explain how this baby had been able to take so much of his mother's blood, 90 c.c. on the second day, without getting some reaction (Baby A, Fig. 4).

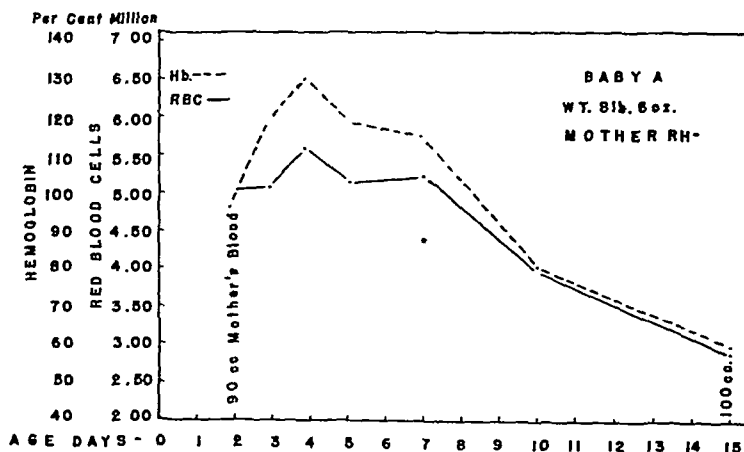


Fig. 4.—Erythroblastosis fetalis, Baby A (Case 1).

CASE 2.—The baby was born in January, 1945. Mrs. S. was a para i, gravida ii, 25 years old, white, Rh negative. The baby was a full-term female child, weighing 9 pounds, 2 ounces, and was given 40 c.c. of mother's blood by cord transfusion. Examination of the blood on the day of delivery showed 3,000,000 red cells; hemoglobin, 82 per cent. The baby was markedly jaundiced. The following day, 125 c.c. of blood from a professional Rh-negative donor of compatible blood group were given. After the transfusion, the red cells were 6,400,000; hemoglobin, 113 per cent. The baby made an uneventful recovery. According to Dr. Levine, this mother had weak anti-Rh agglutinins and weak blocking antibodies.

CASE 3.—Baby L, born Dec. 4, 1944. The mother was Rh negative. She had had a normal baby in 1937, a miscarriage at two and one-half months in 1939, and a baby who died on the third day in 1940. This baby, a boy, weighed 7½ pounds, and condition at birth was good. Examination of the blood showed 3,820,000 red cells; hemoglobin, 60 per cent; 375 normoblasts. The baby was born at 9 A.M.; at 11:30 A.M. 40 c.c. of his mother's blood were given. At 11 P.M. red cells were 3,210,000; hemoglobin, 50 per cent; and 510 normoblasts. Fifty-five cubic centimeters of blood were given. The baby died on the third day. Autopsy showed both liver and spleen enlarged; throughout the liver were clumps of nucleated red cells.

Dec. 4, 1944, the mother was delivered of a supposedly full-term child weighing 5 pounds, 15 ounces. The baby was slightly jaundiced; the spleen, enlarged; and the blood showed 318 normoblasts. It was impossible to give the baby a cord transfusion. Seventy cubic centimeters of blood from an Rh-negative donor were given, and the following day red

cells were 4,800,000; hemoglobin, 90 per cent; nucleated red cells, 63. On December 8, the fifth day, red cells were 3,910,000; hemoglobin, 69 per cent; nucleated red cells, 21. Seventy-five cubic centimeters of blood from an Rh negative donor were given, and the baby made an uneventful recovery.

The baby had a reaction from the second transfusion which looked very serious for a while, but we found that he had had a bottle just before the transfusion, had vomited and aspirated some of his dinner. He was soon all right. We would have given more blood if this had not occurred (Baby L, Fig. 5).

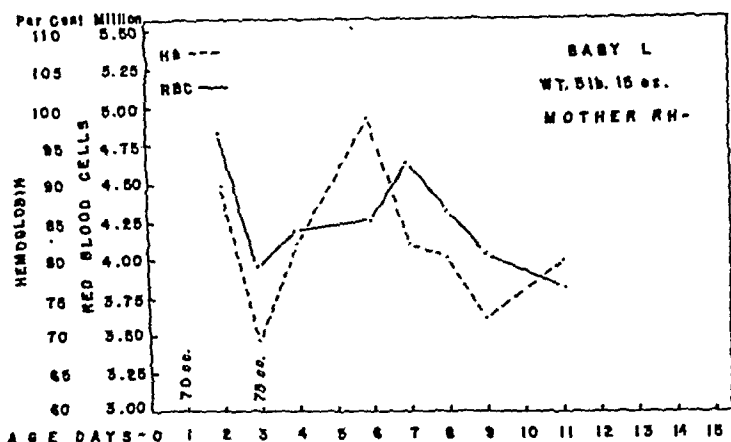


Fig. 5.—Erythroblastosis fetalis, Baby L (Case 3).

CASE 4.—The following case is one in which both parents were Rh positive; it is difficult to explain the loss of three of five babies.

Mrs. D. A. had lost two babies—one at eight months who had lived for twelve hours, one at seven months who lived for five hours. On Sept. 1, 1940, she was delivered at Methodist Hospital of a seven months' baby weighing 4 pounds, 4 ounces; he was transfused through the umbilical cord with 40 c.c. of his father's blood. This baby lived and is now 5 years old and a normal child. This was the first baby to receive a cord transfusion, and the case was reported in 1944, together with the mother's fourth delivery, in June 1943, when she was delivered of a baby weighing 6 pounds, 4 ounces, of thirty-six weeks' gestation. The baby was given a cord transfusion, using his father's blood, but when 20 c.c. were injected, the baby showed signs of a reaction and the transfusion was discontinued. The baby died in twenty-five minutes. Autopsy showed cause of death was hemorrhagic disease.

On March 18, 1945, this patient, now 34 years old and a gravida v, was delivered of a baby weighing 6 pounds, 11 ounces. The baby was given a cord transfusion of 40 c.c. of his mother's blood without any reaction and is apparently a normal baby. During this pregnancy the mother received $\frac{1}{4}$ grain protiodide of mercury twice daily, 20 minims of wheat germ oil daily, and during the last month one milligram of vitamin K daily. She was delivered at thirty-eight weeks, her only pregnancy to go into the ninth month.

NORMOBLASTS FOUND IN CORD SMEARS

The value of cord blood smears taken at birth has not been stressed nor is the significance of an increase in number of normoblasts sufficiently appreciated. The number of normoblasts is supposedly increased in certain conditions, such as diabetes, hemorrhage, and asphyxia; if the mother is Rh negative, we should suspect some blood dyscrasia, possibly erythroblastosis.

In 1944, a study of 538 routine cord smears showed that 279, or 51.9 per cent, contained no nucleated red cells, seventy contained only 1 in 100 white cells; 236, or 43.9 per cent, 1 to 15. There were twenty-three instances, 4.3 per cent, in which more than fifteen normoblasts were found (Table VI).

A study of sixty-three smears from the cord blood of babies of Rh-negative mothers showed considerable difference. Only nine smears, 14.3 per cent, contained no nucleated red cells, only four 1, and forty-three, or 68.3 per cent, from 1 to 15. There were eleven, or 17.5 per cent, that contained more than 15 (Table VI).

TABLE VI. NORMOBLASTS FOUND IN 601 CORD SMEARS

NORMOBLASTS	ROUTINE SMEARS	PER CENT	MOTHERS RH--	PER CENT
None	279	51.9	9	14.3
1	70		4	
2	51		7	
3	26		5	
4	20	43.9	3	68.3
5	15		5	
5 to 10	37		14	
10 to 15	17		5	
15 to 30	12		7	
30 to 40	4		2	
40 to 100	6	4.3	1	17.5
Over 100	1		1	
Total	538		63	

These thirty-four smears with more than 15 normoblasts deserve study (Table VII). In twenty-three the mothers were Rh positive; in eleven, Rh negative; nine of the infants of the Rh-negative mothers received cord transfusions. There were five deaths and one stillbirth among the thirty-four infants; five of the six mothers were Rh positive; one, Rh negative.

TABLE VII. THIRTY-FOUR CORD SMEARS SHOWING MORE THAN FIFTEEN NORMOBLASTS

Rh Factor		Mortality	
Rh-	11	Stillbirth	1
Rh+	23	Died	5
Parity		Lived	28
Primipara	9	Transfusions	
Multipara	25	Cord	9
Gestation		Later	6
Premature	7	None	20
Full-term	27	Duplications	1

The mother of the stillborn child was Rh positive; the baby was full term, weighed 8 pounds, 2 ounces, and had 37 normoblasts. Four mothers of the five infants who died were Rh positive and none of the infants received cord transfusions. One weighed 1 pound, 13 ounces, and had 32 normoblasts. The second weighed 10 pounds, 12 ounces, and had 44 normoblasts; this baby lived only a short time following a difficult breech delivery. The third was full term, weighed 7 pounds, 7 ounces, and lived only one hour. Increase in the normoblasts in these last two cases may have been due to asphyxia. The mother of the fourth baby, also Rh-positive, had had three children, all small, the last

one weighing 5 pounds, 5 ounces. The baby seemed in good condition at birth; when he was 12 hours old he had bloody vomitus. He was transfused with 45 c.c. of his mother's blood but died soon after. Only the mother of the fifth baby was Rh negative, and this baby had had a cord transfusion. He was a premature infant, of thirty-one weeks' gestation, weight was 3 pounds, 9 ounces, and the child was in critical condition at birth and lived only one hour, ten minutes. Cord smear showed 46 normoblasts. The mother was a gravida i, blood group O. The baby was Rh positive, blood group B. At autopsy internal hydrocephalus was found.

Six of the total of eight cases of erythroblastosis or blood dyscrasia diagnosed as erythroblastosis in the 137 infants of Rh-negative mothers occurred in babies with high normoblast count. The two in which there was no increase are (1) the premature infant of thirty-four weeks, delivered by cesarean section and dying within fourteen hours; this infant had received a cord transfusion; (2) the full-term infant in the nontransfused group, markedly jaundiced but with no normoblasts, who died on the fourth day.

SUMMARY

1. A total of 189 cord transfusions were done during 1944 with 174 living babies.

2. Ninety-nine premature babies received cord transfusions of mother's blood, with fourteen deaths. Six of these weighed less than 3 pounds; nine were twenty-eight weeks' gestation.

3. Twenty-one babies were transfused following long labors or difficult deliveries, with no deaths.

4. The blood was grouped and the Rh factor determined in 1,910 women. Of these, 294 were found to be Rh-negative and 137 were delivered in 1944 with the loss of four infants, two in the group of seventy-eight receiving cord transfusions, two in the group of fifty-nine not receiving such transfusions.

5. The babies of seventy-eight Rh-negative mothers received cord transfusions of mother's blood. There were two deaths, both premature infants. Three cases of erythroblastosis were diagnosed in the group, with recovery.

6. Of fifty-nine babies of Rh-negative mothers not given cord transfusions, there were five cases of erythroblastosis, with two deaths. One of the babies was very jaundiced, with no normoblasts; the other had 158 normoblasts to 100 white cells.

7. A study was made of 601 cord smears; 288 contained no normoblasts, thirty-four more than 15. Among these thirty-four infants there were five deaths and one stillbirth. Five of the six mothers were Rh positive; one Rh negative. Of the eleven infants of Rh-negative mothers in the group of thirty-four, nine received a cord transfusion, with one death, a premature infant.

8. A case is reported in which 90 c.c. of blood from an Rh-negative mother of high titer, 1:80, was given to her baby for marked jaundice with definite improvement in the baby's condition.

CONCLUSIONS

During the last five years, we have given 281 cord transfusions to newborn babies with the loss of only twelve viable infants. Our technique has been considerably improved since the beginning, and it is seldom that the transfusion is not successful. We believe that the giving of mother's blood is a means of saving many premature babies and those at term born after a long labor or difficult delivery. The transfused blood tends to overcome anoxia, stimulate the respirations, and give to the premature baby adult red corpuscles which are able to carry oxygen to the tissues.

We are now giving cord transfusions to babies born of Rh-negative mothers when the mothers have had a previous pregnancy. Use of mother's blood rather than donor's is contrary to the general rule, but so far the mother's blood seems to agree with the babies. Cord transfusions may be useful in anticipation of the development of erythroblastosis in infants of Rh-negative mothers or in its treatment when present at birth.

I wish to express my gratitude to Dr. Philip Levine for personal interest and helpful suggestions in editing this paper. Dr. Levine has checked a large number of the blood specimens from Rh-negative mothers.

The great majority of the cord transfusions were given by our resident staff. Dr. Isabelle Seismann, Dr. Norma Jones, and Dr. Frank R. Hurlbutt, Jr., and to them I am deeply indebted.

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494 FIRST STREET

ADDENDUM

There have been 117 additional cord transfusions between April 1, and Dec. 1, 1945. Fifty-three of the transfusions were given to babies of Rh- mothers, using mothers' blood, making a total of 85 such transfusions this year with the loss of no viable babies from these mothers.

The total number of cord transfusions of mothers' blood given to their babies is 398. Two hundred three of the babies were premature and 163 were babies of Rh- mothers.

ANTI RH AGGLUTININS IN THE MATERNAL BLOOD WITHOUT SYMPTOMS OF HEMOLYTIC ANEMIA IN THE NEWBORN INFANT

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THE presence of anti Rh agglutinins in the serum of a pregnant or parturient woman nearly always is followed by a more or less severe hemolytic anemia in the newborn infant. Dockeray and Sachs¹ however have reported four cases in which the mother's sera contained considerable amounts of what were assumed to be anti Rh agglutinins and yet the newborn infants did not exhibit clinically demonstrable manifestations of hemolytic disease. In two of their cases it is not clear whether true anti Rh agglutinins or some other atypical agglutinins were present. In the third case anti Rh agglutinins were present but the records do not state whether the infant's blood was examined for the presence of anemia or hemolysis. In the fourth instance anti Rh agglutinins were found four years after the last delivery and following a transfusion reaction. Four children born prior to this accident gave no history of having suffered from hemolytic anemia. However, a slight degree of jaundice may have been regarded as physiologic or may have been completely overlooked.

We had the opportunity of observing and studying a case in which anti Rh agglutinins were present in the mother's serum although the infant did not demonstrate any of the symptoms of hemolytic anemia of the newborn.

A. C.,* a white woman aged 25 years, was delivered of her third child, a boy weighing 7 pounds, 11 ounces. The delivery was at term and uneventful. Routine testing of the mother's and of the infant's blood revealed:

Mother: group O Rh negative

Infant: group O Rh positive

Tests of the undiluted serum of the mother with several specimens of known Rh positive red cells (including the cells of her own infant) gave a positive reaction ranging in intensity from \pm to $++$, whereas Rh-negative cells did not show any agglutination. The husband and the two older sons (5 and 3 years old, respectively) also belonged to group O and were Rh positive. These two children are reported in the records of the hospital as having been jaundiced from the third and fourth day of life, respectively, until the seventh day. Both children have developed normally and are in good health.

The newborn baby was kept under close observation. No sign of jaundice could be found during the newborn period and none was reported to us later by the family physician. Red cell counts and hemoglobin estimations during the period of hospitalization are listed in Table I.

The van den Bergh reaction done with cord blood showed: direct, 1.13 and indirect, 3.98. The weight of the infant was on the increase when the baby left the hospital. According to current reports the child is progressing normally.

From the Department of Pediatrics and the Pathological Laboratories of the Jewish General Hospital.

*The case history is presented through the courtesy of Dr. J. Goldberg.

TABLE I

	DAY OF LIFE							
	1	2	3	4	5	7	8	9
Number of red cells (Millions/cu.m.)	6.8	6.0	5.2	4.8	5.0	4.8	4.5	4.5
Hemoglobin (Gm./100 c.c.)	20.3	19.3	18.7	18.4	17.5	17.2	18.4	18.1

In a consecutive series of 1,402 deliveries at the Jewish General Hospital in which Rh typing of mother and newborn baby has been performed, the combination of Rh-negative mother and Rh-positive infant was encountered ninety-three times. In each of these cases the serum of the mother was tested for the presence of anti Rh agglutinins, using the infant's red cells (when possible) and several other specimens of compatible Rh-positive cells. Only in the case here reported were anti Rh agglutinins found without any sign of hemolytic anemia in the newborn infant, whereas in eight other cases the finding of agglutinins in the mother's serum was accompanied by a more or less severe hemolytic disease in the baby.

Since anti Rh agglutinins have usually not been demonstrated in the infant's blood by tests *in vitro*, it is difficult or even impossible to determine whether any anti Rh agglutinins have passed through the placenta at least in amounts sufficient to do detectable harm. According to Polayes, Lederer, and Wiener² in only 66 per cent of compatible cases do normal isoagglutinins pass through the placenta. Lubinski³ found a somewhat higher percentage (77.5 per cent of 440 cases). It is therefore possible that the same holds true with regard to the passage of anti Rh agglutinins.

There is a discrepancy between the number of combinations of Rh-negative mother and Rh-positive infant and the frequency of hemolytic anemia of the newborn. Thirteen per cent of all matings involve an Rh-negative mother and an Rh-positive father; yet only 0.25 to 0.5 per cent of all deliveries result in infants showing hemolytic anemia. This requires the consideration of certain variable factors in the pathogenesis of the disease in addition to differences in Rh type.

From a serologic point of view these factors may be listed as follows:

1. The antigenic power of an individual Rh factor may vary, as is true of any antigen. The Rh factor seems to be a relatively poor antigen, an assumption which is suggested by the fact that many transfusions stretched over a period of several weeks or several pregnancies are usually necessary to build up enough antibodies for the development of a severe reaction. A further confirmation of this opinion lies in the fact that it is rather difficult to obtain anti Rh sera from animals through artificial immunization.

2. The ability of an individual to produce antibodies is well known to vary greatly as in natural immunization through disease, or by artificial immunization through vaccination. This applies as well to immunization by the Rh factor.

3. The amount of antigen that enters the maternal circulation may vary in different cases and may be nil in some. Some authors assume that damage to the placental barrier is necessary for the transmission of the antigen. This

opinion is open to question, chiefly because if this were true, such damage must be assumed in each successive pregnancy in which hemolytic anemia occurs. Moreover, if this were true, a mother with a blood group incompatible with that of her fetus should show a great increase in the titer of normal isoagglutinins; but this is not a common observation.

4. The amount of antibody which passes through the placenta from the mother's circulation into the blood stream of the fetus varies widely in different cases. This is illustrated by the fact that the titer of normal iso- and hetero-agglutinins found in cord blood varies greatly. According to Wiener and Silverman⁴ the proportion of titers in maternal blood compared to the titers in cord blood is generally between 8:1 and 12:1. However, one of us (L) has found (in a series of experiments to be published elsewhere) that wider variations from the average than those given by Wiener and Silverman can be found not infrequently. Two of the most striking examples are given in Table II.

TABLE II

TITER OF ISOAGGLUTININS		TITER OF ISOAGGLUTININS		RATIO
Case 1136	1/16 000	Case 1136	1/16	1000
Mother	1/512	Baby	1/1	512
Case 1453	1/8	Case 1453	1/2	4
Mother	1/256	Baby	1/1	256

Furthermore, it seems that a continuous flow of small amounts of antigen over a long period is of greater importance in the causation of the hemolytic disease than the influx of large quantities over a short period.

5. Unknown factors in the fetus, which may be called disposition, seem to be of importance as well. This is clearly shown by Demy's case,⁵ in which identical twins of about the same weight reacted quite differently: one infant was severely ill, while the other did not even require a transfusion and showed hardly any clinical signs of disease. It seems unreasonable to assume a difference in the transmitted quantity of antibodies as the cause of differences in the clinical picture. In a small number of tests, identical twins have shown identical titers of normal antibodies.³

SUMMARY

A case is presented in which the Rh-positive infant of an Rh-negative mother demonstrated no clinical or laboratory evidences of a hemolytic anemia of the newborn, although anti Rh agglutinins were shown to be present in the maternal blood at the time of delivery.

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EPIDEMIC MENINGITIS AND MENINGOCOCCEMIA TREATED WITH PENICILLIN

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DURING the past year twenty-one patients with meningococcus infections were treated with penicillin intrathecally and intramuscularly or intramuscularly alone in the Division of Contagious Diseases at City Hospital, Cleveland.

The clinical course, the temperature, the decrease of the number of cells in the spinal fluid toward normal levels and the findings in spinal fluid cultures became the criteria whereby it was decided to continue with penicillin or to change the therapy.

In our first series, there were fourteen patients ill with epidemic meningitis. Eleven had positive spinal fluid smears on admission; eleven, positive spinal fluid cultures; three, positive blood cultures; and eight had petechiae. One patient had petechiae only; the other thirteen had either a positive smear or culture, or both.

The first eleven of these patients were given from 10,000 to 15,000 units of penicillin intramuscularly every three hours. Rosenberg and Arling¹ reported that 15,000 units of penicillin given intrathecally caused irritation and meningeal signs. Therefore, only 10,000 units were administered intrathecally in the first eleven cases of this study, the greatest number of intrathecal injections being five and the least three. Three subsequent patients were given daily intrathecal injections of 20,000 units each. The last 3 were given 20,000 units every three hours and 20,000 units intrathecally daily. Two of these had four injections and one only two when the treatment had to be changed. Eight of these fourteen cases responded satisfactorily to intrathecal and intramuscular administration of penicillin, while six did not respond so well. A brief summary of each of the latter cases follows.

PATIENT 1.—J. R. (Case 263264), a white female, aged 22 years, had 38,750 cells in the spinal fluid on admission and a positive spinal fluid smear and culture for meningococci. She was comatose and had numerous petechiae. She was given 10,000 units of penicillin intrathecally for four successive days and 10,000 units intramuscularly every three hours during that time. She was still critically ill at the end of the second hospital day when she was given 100,000 units of meningococcic antitoxin. She showed no response clinically on the fourth day even though the spinal fluid contained only 321 polymorphonuclear cells. Treatment was changed to sulfadiazine on the fifth day; on the sixth hospital day consciousness returned and the temperature began to drop by lysis. This patient had partial deafness.

PATIENT 2.—E. M. (Case 263299), a 14-year-old Negro male, was admitted conscious but with a severe headache. The admission spinal fluid contained only 12 mononuclear cells, from which meningococci were cultured. Blood culture was also positive. He was given 15,000 units of penicillin daily for three days and 10,000 units intramuscularly every three hours. The temperature spiked for five days, dropping slowly to 37.8° C. on the sixth hospital day. Later that day, the temperature suddenly rose to 39° C. and he seemed worse clinically. Penicillin

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was discontinued and sulfadiazine started. His temperature was normal on the next day and remained at normal levels.

PATIENT 3.—M. H. (Case 263664), a 38-year-old white female, was admitted in a comatose condition with 13,750 cells in the spinal fluid, from which organisms were cultured. She was given a daily intrathecal injection of 10,000 units of penicillin for 5 days and 15,000 units intramuscularly every 3 hours. She had positive cultures up to and including the fifth day when 1,100 cells were found in the spinal fluid. The patient was conscious on the second hospital day, but she had a constant headache and the temperature averaged 38.5° C. for six days following admission. On the sixth hospital day, the treatment was changed to sulfadiazine. The headache disappeared the next day and the temperature dropped to normal, where it remained.

PATIENT 4.—P. F. (Case 264343), a 50-year-old white male, was conscious on admission and had a temperature of 37.4° C. He had 11,150 cells in the spinal fluid and the smears and the cultures were positive. He was given 10,000 units of penicillin every day for three days and 15,000 units intramuscularly every three hours for four days. The temperature rose steadily to 39.4° C. and on the fourth hospital day the patient's condition became worse and he was wildly delirious. There were 5,000 cells in the spinal fluid on the third hospital day. Sulfadiazine was started on the fourth hospital day and the penicillin discontinued. The temperature became normal by the following evening and remained thus thereafter.

PATIENT 5.—P. K. (Case 220431), a 5-year-old white female, was admitted with a history of having had an acute illness resembling meningococcemia. The spinal fluid smear and culture were negative on admission. The blood culture was positive. The temperature was 40.5° C. She was given penicillin, 20,000 units intramuscularly every three hours and 20,000 units intrathecally for two days. On the second hospital day, she became comatose and wildly delirious. The spinal fluid at this time contained 6,400 cells and the smear and culture were positive. There were more petechiae than on admission. On the third hospital day, the spinal fluid showed 8,000 cells and smears were positive. The temperature was 38° C. and the patient was deeply comatose. Treatment was changed to sulfadiazine and meningococcic antitoxin, 50,000 units of which were given on the afternoon of the third day. She began to respond and was only delirious for a time on the fourth hospital day. She was alert on the fifth hospital day and had a normal temperature thereafter.

PATIENT 6.—W. L. (Case 267946), a 46-year-old white male, was admitted delirious and in a comatose condition with a temperature of only 37.9° C. The spinal fluid contained 45,000 cells and the smear and the culture were positive. He was given 20,000 units of penicillin intrathecally for four days and 20,000 units intramuscularly every three hours for the same period of time. He appeared to be the same clinically on the second hospital day and there were 20,000 cells in the spinal fluid. On the third hospital day his temperature rose slightly and, clinically, he was worse, although the number of cells in the spinal fluid dropped to 8,000. It was decided to continue the same treatment. On the fourth hospital day, the temperature rose to 39.8° C. He became deeply comatose and appeared to be moribund. The spinal fluid contained only 2,740 cells, but because of his desperate condition the treatment was changed to sulfadiazine and 100,000 units of meningococcic antitoxin. On the fifth hospital day, he began to respond clinically. On the sixth and seventh hospital days, he was alert again, the temperature still being near 39° C. On the eighth hospital day, he began to have some slight deafness. By the tenth hospital day he was completely deaf. The temperature began to fall, averaging about 38° C. until the fourteenth day, and it was at normal levels by the eighteenth hospital day. On that day and for the next two days, he had periods of hallucinations which cleared by the twentieth hospital day.

It was felt that possibly an inadequate amount of penicillin had been given to these eleven patients, so that the dosage both intramuscularly and intrathecally was raised to 20,000 units in the next three patients. In spite of this, difficulties in treating these patients were encountered as with the preceding

patients. Further, a clear-cut case of meningococcemia progressed on to purulent meningitis, a meningitis not prevented by penicillin in the dosages used.

In this small series, some patients did not respond to penicillin therapy. Our observations are that patients treated with penicillin respond more slowly than do those treated with sulfadiazine and antitoxin, the standard treatment in our hospital.²

In a series of four patients, the meningitis was treated with penicillin intramuscularly only. A brief summary of each of these cases follows.

PATIENT 15.—C. S. (Case 266674), a 2½-year-old white male, was admitted acutely and seriously ill, but conscious. There were only 60 cells in the spinal fluid, all of which were polymorphonuclears. He had petechiae and the blood and spinal fluid cultures were positive. He was given penicillin, 15,000 units every three hours for a total of 390,000 units. The temperature was 40° C. on admission and dropped to 37° C. in thirty hours and he was clinically better. The spinal fluid at that time contained 4,000 cells, all being polymorphonuclears. Up to the fifth hospital day, he had a low-grade fever between 37.5° C. and 38° C. On the sixth hospital day, a lumbar puncture showed 124 cells, 60 per cent of which were monocytes. He was discharged by release on the eighth hospital day, clinically cured.

PATIENT 16.—J. L. (Case 266775), a 38-year-old white female, entered the hospital acutely ill and somnolent, although she could be aroused. She complained of severe headache. The spinal fluid obtained on admission showed 4,900 cells, 94 per cent of which were polymorphonuclears. Culture and smears of the spinal fluid were positive for meningococci. She was given penicillin, 15,000 units every three hours for a total of 840,000 units. Clinically she made a fair response, although the temperature curve went up and down, becoming normal for a short time on the fifth hospital day, after which it remained close to 38° C. Up to and including the seventh hospital day, the patient complained repeatedly of a severe headache. The spinal fluid at this time contained 2,180 cells, 95 per cent being polymorphonuclears. The smears were negative, but the culture was positive. On the eighth hospital day, she was given sulfadiazine and her headache disappeared by the next day. On the ninth hospital day, the temperature was normal and remained unchanged until discharge.

PATIENT 17.—J. S. (Case 266904), a 38-year-old white male, was admitted in a wildly delirious condition. The spinal fluid contained 14,750 cells, all being polymorphonuclears. The smear and the culture were positive. On the second hospital day, the patient was quieter, but on the third hospital day he was alternately comatose and delirious, his condition becoming much worse. The spinal fluid at this time showed 2,000 cells. He had been given penicillin intramuscularly 15,000 units every three hours during this time and it was decided to continue the therapy. On the fifth hospital day he appeared no better. The spinal fluid contained 1,200 cells with many meningococci on direct smear. The treatment was changed to sulfadiazine and antitoxin after a total of 435,000 units of penicillin. The next day, which was the sixth hospital day, he was clinically improved, although somewhat disoriented. By the eighth hospital day, his temperature was normal, he was well oriented, and recovery was uneventful.

PATIENT 18.—R. B. (Case 267025), a 43-year-old Negro male, entered the hospital severely ill, toxic, semicomatose and delirious. The temperature was 38.8° C. on admission. There were 9,200 cells in the spinal fluid, all of which were polymorphonuclears and the smear and the culture were positive. He was given 15,000 units of penicillin intramuscularly every three hours. The temperature came down precipitously the next day, although the patient was worse clinically. On the third hospital day the temperature rose again to 39.9° C. Another spinal fluid was obtained and it contained 10,250 cells, all polymorphonuclears, but no organisms were seen. However, a culture of the spinal fluid was positive on the next day when the treatment was changed to sulfadiazine and antitoxin. A total of 240,000 units of penicillin had been given. The patient remained in a delirious and comatose state. The course was downhill and he died on the evening of the ninth hospital day following a generalized convulsion.

In these four cases, one patient bordered on a meningococcemia or very early meningitis, one was moderately ill, and two were very seriously ill.

Four patients with meningococcemia were treated with penicillin administered intramuscularly.

PATIENT 19.—A. F. (Case 264832), a 20-year-old white female, was a sister to a patient in the hospital with proved epidemic meningitis. The spinal fluid and the culture were negative. The blood culture was positive. The temperature on admission was 40.9° C. She was given 15,000 units penicillin every three hours for a total of 345,000 units intramuscularly. She improved rapidly and her temperature was normal within two days and remained thus thereafter. She was discharged by release on the sixth hospital day.

PATIENT 20.—G. L. (Case 267202), a 2½-year-old white female, was acutely ill on admission with a history of having been ill only twelve hours previously. She had numerous petechiae in the skin. The spinal fluid was negative. Blood culture and smears from the petechiae were positive for meningococci. Penicillin was given intramuscularly, 15,000 units every three hours for a total of 645,000 units. The response was excellent and within twelve hours after therapy was started. She was discharged on the seventh hospital day.

PATIENT 21.—V. E. (Case 267789), a 4-year-old white male, was admitted acutely ill, slightly delirious with a generalized petechial rash, stiff neck, and temperature of only 37.7° C. He became ill approximately eighteen hours before admission. The lumbar puncture was negative. Smears of the petechiae were positive for meningococci. Twenty thousand units of penicillin were given intramuscularly every three hours for a total of 700,000 units. The temperature became normal in twelve hours and he was discharged on the ninth hospital day.

PATIENT 5.—P. K. was the patient previously described. She had meningococcemia which progressed to meningitis despite the use of penicillin intrathecally.

SUMMARY

Twenty-one patients with proved meningococcal infections were treated with penicillin.

A. Fourteen of these patients had epidemic meningitis and were treated with penicillin intrathecally and intramuscularly. Eight patients responded satisfactorily; six did not respond so well to the doses administered.

B. Four patients ill with epidemic meningitis were treated with penicillin administered only intramuscularly. Of these, three did not respond too well to therapy and one died.

C. Four patients had meningococcemia and were treated with penicillin intramuscularly. Three recovered promptly. In one patient, the infection progressed to epidemic meningitis.

CONCLUSION

The daily intrathecal and frequent intramuscular administration of penicillin is a tedious procedure. To us the results are not of sufficient value to warrant its use as a form of treatment in epidemic meningitis when simpler and more effective methods are available.

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USE OF AMINO ACIDS IN A CASE OF SEVERE *SALMONELLA* SCHOTTMUELLERI (PARATYPHOID B) INFECTION IN AN INFANT

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SALMONELLA schottmuelleri (paratyphoid B) infection in infants is not common. Except for reports of isolated cases, the literature on sporadic cases of infections due to *Salmonella* in infants is quite limited. A recent investigation reported by Neter¹ describes twenty cases of sporadic infections in infants. It took three years to collect these in a comparatively large-sized hospital in a large city. Of these twenty cases, only two proved to be of the schottmuelleri or paratyphoid type of infection. Investigations by Kauffman in Denmark, of Hormaeche in Uruguay, and Edwards, Shiff, Seligmann, Bornstein and Saphra in the United States, have added to the material knowledge of *Salmonella* infections in human beings. Most of the work on this disease has been done recently. Investigation of the older literature is very unsatisfactory. It is interesting to note that Finkelstein, the renowned European pediatrician of previous decades, stated that he had never observed a case of *S. schottmuelleri* infection in an infant under one year.² In general, this disease was not considered to be a serious one in children, although Neter, in the article previously referred to, described four fatalities in his report of twenty cases, and it was his opinion that the disease is not necessarily a benign one. However, Seligmann and Hertz³ reported eight cases due to *Salmonella* in infants without fatalities. Numerous complications have been reported such as meningitis,⁴ peritonitis,⁵ and osteomyelitis,⁶ as well as four cases with unusual complications described by Freedman⁷ such as acute hydrops of the gall bladder, empyema, cavernous sinus thrombosis, and uremia (liver failure).

Treatment of the disease is not specific and has been more or less of the symptomatic and supportive type. It is the purpose of this paper to emphasize a phase of the supportive therapy by presenting a case report of a severe *S. schottmuelleri* infection in an infant, with recovery.

CASE REPORT

A 15-month-old male child, one of a set of paternal twins, premature at birth, was admitted on August 21, 1944, to an Army regional hospital in Georgia. Profuse diarrhea had been present for five days prior to admission, which was followed by vomiting the night before admission. He had retained little or no fluid for the past twenty-four hours. The skin was dry and the patient appeared somewhat emaciated. The turgor was poor and some hyper-tonus of the musculature was noted. The child had just returned with the parents from a trip to Mississippi and had been exposed to unusually hot sultry weather, and according to the father's history, had had some unpasteurized milk. Further physical examination revealed a listless, weak child, unable to take nourishment by mouth. The chest was clear, eyes, ears, nose and throat appeared normal; there was no rash present. Laboratory examinations re-

vealed 12,650 white blood cells of which only 37 per cent were polymorphonuclear and 63 per cent were lymphocytes. The hemoglobin was 13.5 Gm. The urine showed 4 plus albumin, occasional white blood cells and red blood cells as well as occasional hyaline and granular casts. Rectal temperature was 100° F., respirations were rapid and shallow. Fluids in the form of 250 c.c. of normal saline were administered intraperitoneally. Shortly after this small amounts of fluid were taken by mouth, but were soon vomited. Diarrhea continued to persist. The stools were watery and green. The first night was spent restlessly in spite of bromide sedation given by rectum. The following day the patient was started on a kaomagma-banana regime. The temperature rose to 103° F. Sulfadiazine therapy was begun but the general condition did not improve. On the third hospital day, August 23, a convulsion lasting three minutes occurred. In order to administer parenteral fluids, it was necessary to have the surgeon cut down on an ankle vein. A trocar was inserted and 2½ per cent glucose in normal saline was administered. Shortly thereafter a second convulsion occurred and it was then that pediatric consultation was requested in view of the lack of response to therapy as well as the progression of severity of symptoms.

Examination at this time showed the child to be in the midst of a convulsion; cyanosis and episthotonos were marked; exophthalmos and nuchal rigidity were present. All deep reflexes were exaggerated. There were definite signs of increasing meningoencephalopathy as a result of the severe toxicity. A transfusion of 100 c.c. of citrate of blood was given and resulted in only a slight immediate response. At this time the rationale of administering amino acids was considered in view of the explanation of a greater part of the toxicity being due to some liver damage. It is not uncommon to find on autopsy advanced liver damage in severe dyspepsia, especially in the so-called Finkelstein's intoxication. Consequently, after the transfusion, 30 c.c. of parenteral amino acids were added to 100 c.c. normal saline and given intravenously. There was no untoward effect and the response was dramatic. The child appeared much brighter within one-half hour after the administration of the amino acids, moved about more easily, reacted to sound and stimuli, and appeared to have a definite decrease in musculature hypertonus. The meningismus gradually subsided and the general toxic condition was greatly reduced. The stools soon after appeared less watery, became less frequent, and showed signs of a more normal appearance. In view of the dramatic improvement noticed after the administration of the amino acids, it was decided to repeat the procedure the following day and also attempt to give some amino acids by mouth with boiled water at intervals, which was somewhat successful. A formula of lactic acid milk was started also and well taken. All this time stools were being sent to the laboratory for culture, and on August 27, the seventh hospital day, a stool was reported positive for *S. schottmuelleri* and confirmed by agglutination with anti-Salmonella schottmuelleri serum. Spot agglutination tests for *S. schottmuelleri* were positive to 1 to 160 dilution on the ninth hospital day (second week of the illness). Stools were repeatedly positive for *S. schottmuelleri* again on the ninth hospital day. Verification of laboratory findings were made by agglutination with the anti serum of *S. schottmuelleri* as well as differential reaction with sugars. The blood agglutinated *S. schottmuelleri* serum up to 1 to 160 dilution. The stools and the urine became negative on September 5, the sixteenth hospital day, but the agglutination titer of the blood increased up to 1 to 320 dilution by this time.

The response to the second administration of parenteral amino acids was as dramatic as the first one. The patient showed sudden improvement. The stools practically became normal in appearance and reduced to normal frequency. The lactic acid formula was taken very well and by the eleventh hospital day Pabulum, Jello, and custard were added to the diet, and later small amounts of ice cream were well tolerated. By the fifteenth day the stools were normal and regular diet was given. The baby was discharged as recovered on the nineteenth hospital day.

It is of interest to note that sulfaguanidine was tried in ½ Gm. doses every four hours for three days, but it failed to render the stools free of the infecting organism.

SUMMARY

1. The incidence of *Salmonella* infections in infants is not very high. The literature on the subject is not abundant, especially with specific reference to the *schottmuelleri* type of infection.

2. The disease, when found, was usually not considered to be a very severe one in infants, although various complications have been reported.

3. A case of severe infection with *S. schottmuelleri* in an 18-month-old child is presented.

4. The dramatic response attributed to the administration of parenteral amino acids as added supportive therapy was considered of general interest to warrant presentation of the case.

CONCLUSION

The value of amino acids as additional supportive therapy in the treatment of *S. schottmuelleri* infections in children, as well as other infectious diarrheas, appears to be deserving of consideration and should be further studied.

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ACUTE GASTRIC ULCER WITH PERFORATION IN ONE OF PREMATURE TWINS

REPORT OF A CASE

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BIRD, Limper, and Mayer¹ have collected the reported cases of peptic ulceration of the stomach and duodenum in infants and children. In 243 cases they found fifty-one infants in the age group from 15 days to 1 year, and of these only eight were gastric. To this group we wish to add another case which may be of particular interest because it occurred in one of premature homologous twins.

A. O. was born in the eighth month of gestation, reported to be homologous although the placenta was not examined microscopically, following an uneventful pregnancy and normal delivery, the first of homologous twin boys. His weight at birth was 3 pounds, 10 ounces. Physical examination was negative except for prematurity, and his condition was reported as good. For the first day the babies were fed glucose water at two hourly intervals and subsequently olac, from 2 to 4 oz. Their courses were parallel until the ninth day when A. O. vomited thick green mucus and his cry became listless. The following day his weight was 3 pounds, 1 ounce, as compared with 3 pounds, 4½ ounces of the twin. From this time on he frequently refused feedings or retained them with difficulty, vomited his formula intermittently, became sallow and progressively weaker until death on the fifty-fifth day. His twin gained weight, grew stronger, and was discharged in good condition on the sixty-second day. Both received a formula of milk, water, and dextrimaltose after the twelfth day, thiamine chloride 75 mg. daily after the tenth day, and ascorbic acid, 25 mg. daily, after the thirty-third day. On the thirty-sixth day A. O. vomited a small amount of brownish fluid. At this time his hemoglobin was 15.8 Gm. Several days later vomiting became projectile. His stools were noted to be dark brown on the forty-fourth day and continued so until the end. They varied in number from none to three per day. Blood count about this time was as follows: hemoglobin, 10.3 Gm.; red cells, 2,380,000; color index, 1.18; white cells, 13,150; polymorphonuclears, 25 per cent; lymphocytes, 69 per cent; eosinophiles, 2.5 per cent; monocytes, 1 per cent; smudged cells, 2.5 per cent. Breast milk which had been given intermittently from the fifteenth day replaced the formula completely during the last two weeks. Roentgenograms taken on the forty-seventh day showed a large, gas-filled stomach with some gas in the small intestine. There was marked retention of barium in the stomach after three hours as compared with emptying time in the twin. The last week he was lavaged with soda bicarbonate, and gavage feedings of breast milk preceded by atropine were given. On the day preceding death it was noted that 30 c.c. of the lavage could not be returned. Throughout his course clyses were administered frequently and intramuscular blood was given three times. Aminoids, 1 teaspoon twice a day, was given the last three days. The temperature paralleled that of the twin until the forty-ninth day when it dropped to 95° F., and it varied from this to 100° F. until he expired. Weight two days before death was 4 pounds, 3 ounces, that of the twin 5 pounds, 5 ounces. At this time, however, the infant appeared malnourished and was edematous.

At autopsy, three hours *post mortem*, a large perforated gastric ulcer was found which involved about one-sixth of the gastric mucosa, similar grossly to the common peptic ulcer of adults. It was situated on the lesser curvature, 1 cm. from the pyloric valve, almost encircling the pylorus. The edges were rolled and the central ulcerated area depressed. Per-

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foration had occurred at the proximal edge on the superoanterior aspect of the stomach near the liver. The gastric mucosa elsewhere was pale and somewhat thickened as was the muscularis of the stomach and of the pyloric valve. A plastic exudate was found over the surface of the liver, spleen, and along the descending colon and in the pelvis, and a small amount of purulent fluid was present in the abdominal cavity. The spleen appeared somewhat enlarged with a tense capsule. Other abdominal organs were not remarkable. In the thoracic cavity a few cubic centimeters of yellowish fluid was present on each side, that on the left containing some flecks of fibrinopurulent exudate. The lungs were reddened in their dependent portions but without consolidation. Excess fluid was found in the pericardial sac. There was edema throughout the areolar tissue in the mediastinum, mesentery, and retroperitoneal tissues, as well as in the lower extremities. Microscopic examination through the ulcer at the point of perforation showed an acute process with no attempt at repair. The edges of the perforation were necrotic, but there was little inflammatory reaction except for the exudate on the peritoneal surface.



Fig. 1—Stomach of infant after alcoholic fixation showing large ulceration on lesser curvature with site of perforation (marked by arrow) at proximal border.

COMMENT

The etiology in this case, as in the majority occurring in infants, is obscure. Predisposing factors mentioned by Guthrie² and others are lacking. Labor was uneventful and delivery normal. There were no congenital anomalies, nor did the infant have an exanthematous disease or suffer any injury or burns. The role of thiamine chloride and ascorbic acid as irritants seems to be excluded by their simultaneous administration to the twin. Smythe³ has reported two cases occurring in premature infants. Our case also was a premature infant, but it is interesting to note that the twin on the same regime remained well. Crawford and Stewart⁴ saw two cases complicating erythroblastosis fetalis. There was nothing in the history or in the post-mortem findings to suggest such a condition in this infant.

The first and most constant symptom was vomiting beginning on the ninth day. The brown stools and dark vomitus with the appearance of anemia may have indicated that there was bleeding dating probably from about three weeks before death, and on the day preceding death the perforation may have occurred as indicated by the failure to recover a quantity of the lavage fluid. At no time did the infant exhibit any sign of pain. He was considered to have pyloric stenosis and treatment was directed accordingly. Surgery seemed inadvisable because of the size of the infant and his condition. X-ray examination appeared to verify this diagnosis and failed to reveal the ulcer. In this connection Burdick⁵ has pointed out the value of fluoroscopic examination in rendering a positive diagnosis. It would be difficult if the diagnosis had been made to imagine any medical treatment succeeding where breast milk and soda bicarbonate failed. Bird, Limper, and Mayer¹ have emphasized the possibility of surgery in ulcers in childhood and, in this case surgery might have offered the only hope of recovery.

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PAROXYSMAL TACHYCARDIA

REPORT OF TWO CASES IN INFANTS

EDWIN P. SCOTT, M.D., AND MARGARET A. LIMPER, M.D.

LOUISVILLE, KY.

WHILE cases of paroxysmal tachycardia in early infancy are being recognized with increasing frequency, comparatively few cases have been reported. We wish to add two cases, one with a fatal outcome, and one with recovery.

CASE 1.—J. R., a 5-month-old white male infant was admitted to the Children's Free Hospital Sept. 28, 1942. According to the parents he was perfectly well up to ten days prior to admission, when he began to vomit. Intermittent vomiting continued up to hospitalization. The mother was told by several physicians that the infant's heart was "very fast" and that his "liver was enlarged."

Physical examination on admission revealed a well-developed and well-nourished white male infant in slight respiratory distress with a peculiar ashen gray color of the skin. The rate of the heart was extremely rapid, and respirations were shallow and 60 per minute. The liver was palpated three fingerbreadths below the right costal margin. The remainder of the physical examination was not remarkable.

The electrocardiogram revealed a supraventricular tachycardia with a rate of 250 per minute (Fig. 1, A).^{*} There was marked passive congestion in both lung bases on the chest roentgenogram. A complete blood study showed a red blood cell count of 4,790,000 per cubic millimeter with hemoglobin of 94.1 per cent, and a white blood cell count of 13,500 per cubic millimeter with a differential of 43 per cent polymorphonuclear leucocytes, 50 per cent lymphocytes, and 7 per cent "stabs." A complete urinalysis was negative.

After a negative scratch test for quinine dihydrochloride, ½ grain was given intramuscularly, and no decrease in heart rate was noted. Two hours later 1 grain was given intravenously, and again no change could be demonstrated in the heart rate.

The following day, September 29, 2 grains of quinine dihydrochloride were given intravenously without immediate effect; however, when the infant was examined one-half hour later, the heart rate was 125 per minute. Soon the respirations became slower, the liver receded, and the ashen color of the skin disappeared.

The infant was observed for a period of five days and discharged on oral cocoa-quinine.

Numerous attempts were made for follow-up studies, but all were unsuccessful.

On the night of March 5, 1943, six months after the previous admission, the child was readmitted with a history of restlessness and intermittent vomiting of eight days' duration.

Physical examination revealed a well-developed, 11-month-old infant with an ashen gray color to the skin, respiratory rate of 48 per minute, rapid heart, and enlarged liver. The remainder of the physical examination was essentially negative.

Electrocardiogram† revealed paroxysmal ventricular tachycardia with a rate of 239 (Fig. 1, B).

After a negative skin test he was given 2 grains of quinine dihydrochloride intravenously, and a repeat electrocardiogram revealed no change. Six hours later 3 grains were given intravenously, and there was a sudden change of rhythm. Electrocardiogram made 90 seconds after injection revealed a rate of 165 with the QRS complex slurred and prolonged (Fig. 1, C).

From the Department of Pediatrics, University of Louisville School of Medicine.

^{*}Prepared and interpreted by Dr. Emmet F. Horine.

†Prepared and interpreted by Dr. John Walker Moore.

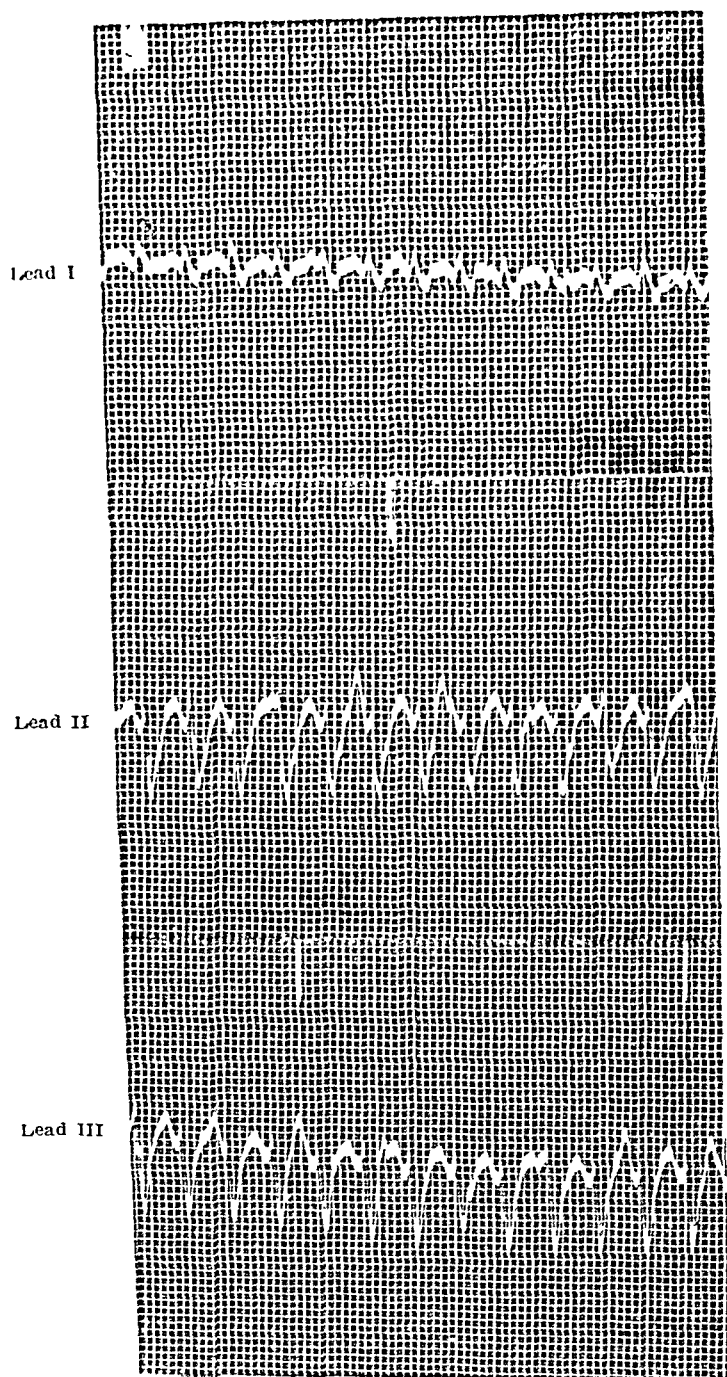


Fig. 1A.—Case 1. Supraventricular paroxysmal tachycardia. Rate 250.

Two hours after the injection of 3 grains of quinine dihydrochloride, the heart was again extremely rapid, with a rate of 239. In view of the return of the tachycardia, 4 grains of quinine dihydrochloride were given intravenously. About two minutes after injection the infant became restless and seemed to have laryngeal spasm. The heart continued to beat for several minutes, but the respirations could not be re-established, despite all emergency measures.

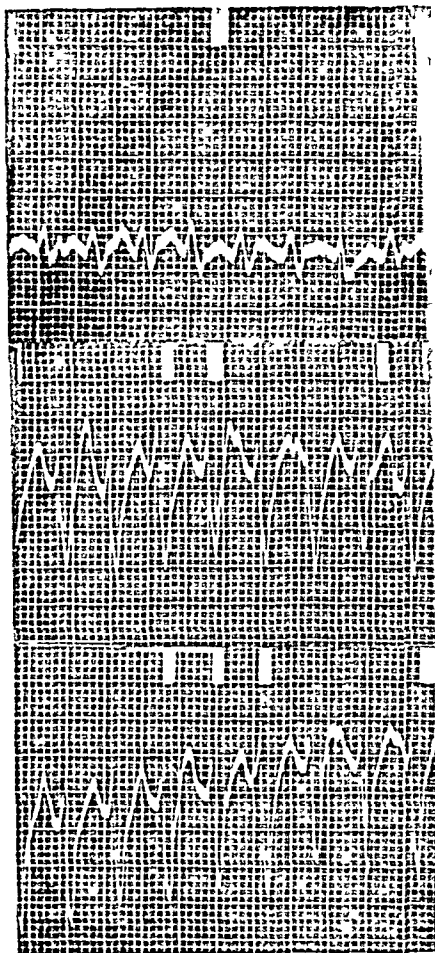


Fig. 1B.

Fig. 1B.—Case 1. Paroxysmal ventricular tachycardia. Rate 239.

Fig. 1C.—Case 1.—Ninety seconds after 3 grains of quinine dihydrochloride were given intravenously. Rate 165.

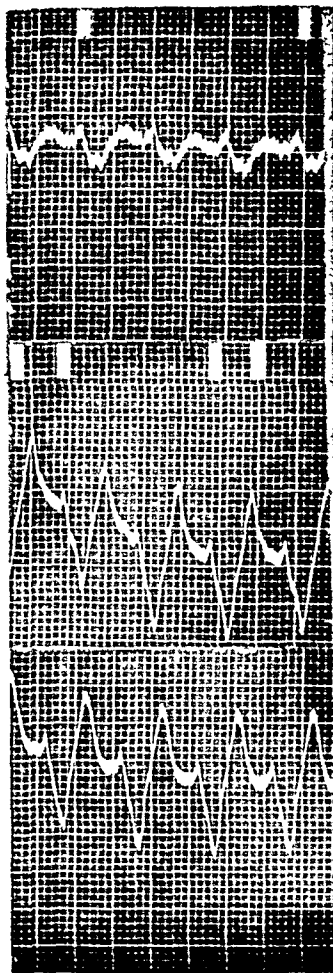


Fig. 1C.

An electrocardiogram taken after respirations had ceased revealed a heart rate of 215. The QRS complex seemed to be longer on this tracing than on any of the previous records.

No autopsy was obtained.

CASE 2.—This 39 day-old male infant was admitted to Children's Hospital Feb. 10, 1944. The infant had been brought to see one of us (M. A. L.) for a routine examination. The heart rate was estimated to be above 200, paroxysmal tachycardia was suspected, and the infant was referred for electrocardiography. A supraventricular type of paroxysmal tachycardia, with a heart rate of 270, was found (Fig. 2, A*). The infant was referred to the hospital.

*Prepared by Dr. Max L. Garon.

Past history revealed that the infant was full term, with a birth weight of 7 pounds, 9 ounces. He was the second child, and the parents and the older brother were healthy. His delivery had been normal. He was not examined by a pediatrician during the newborn period. He had developed impetigo during his hospital stay, and the mother had treated

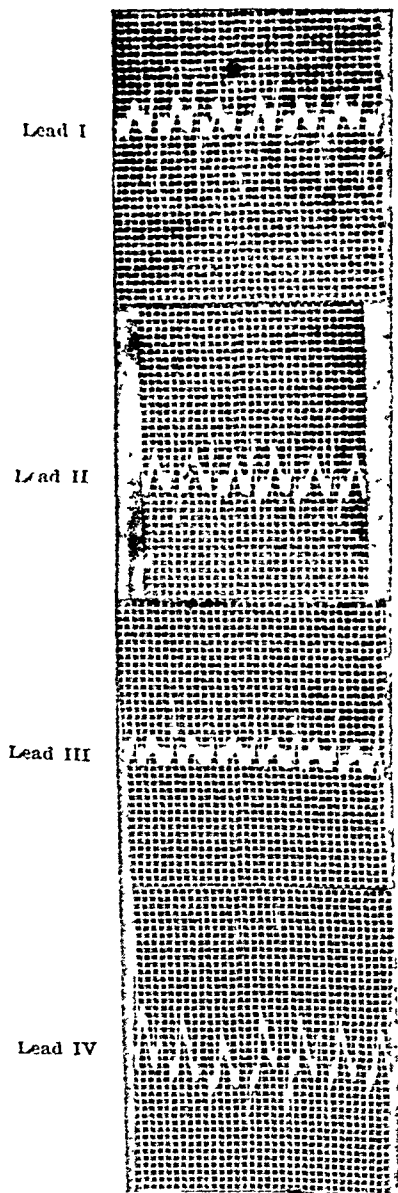


FIG. 2A.

Fig. 2A.—Case 2. Supraventricular paroxysmal tachycardia. Rate 115.

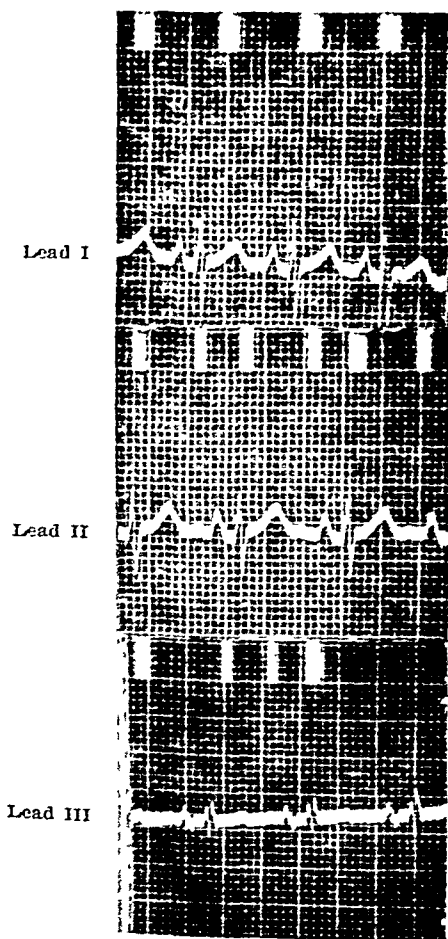


FIG. 2B.

Fig. 2B.—Case 2. Rate 270.

the condition rather overenthusiastically by breaking the vesicles with an alcohol sponge, applying sulfathiazole powder, and changing the infant's clothing every four hours. Alcohol had also been used on the infant's breasts because of engorgement. The infant was receiving

a formula of evaporated milk, water, and corn syrup, supplemented with cod-liver oil and orange juice.

Physical examination revealed a well-developed and well-nourished 9-pound baby with an extremely rapid heart. The heart sounds were loud and booming; otherwise, the cardiac examination was not remarkable. On abdominal examination, the spleen could not be felt, and the liver was palpable but not enlarged. The temperature was 99.2° F., and the respirations 60 per minute. The infant's color was good at the time of admission to the hospital. (When seen in the office, he had an attack of hiccups and exhibited slight transient cyanosis.)

A complete blood study showed a red blood cell count of 3,860,000 per cubic millimeter, with a hemoglobin of 12.5 Gm. per 100 c.c. of blood, and a white blood count of 9,950 per cubic millimeter, with a differential of 62 per cent polymorphonuclear leucocytes, and 38 per cent lymphocytes.

On admission, the infant was given 1.5 grains (0.1 Gm.) of digifolin intramuscularly. Four hours after admission, the infant developed a cyanotic attack but responded readily to oxygen. About five hours after the digitalis had been given, the infant was examined and tachycardia was still present, although the rate seemed to be somewhat slower. Eight hours after admission the heart rate had dropped to 114 per minute. Following this, convalescence was uneventful. A routine electrocardiogram made Feb. 17, 1944, revealed a rate of 115 per minute. (Fig. 2, B.*) The infant was discharged February 18, and repeated examinations over a period of a year have shown no recurrence of the tachycardia.

COMMENT

The first patient (Case 1) was a critically ill infant on both of his admissions, and his second attack of paroxysmal tachycardia with congestive failure might have ended fatally under any circumstances. Paroxysmal tachycardia in Case 2 was observed more or less accidentally, before any symptoms or signs of congestive failure had appeared. In such cases patients occasionally recover without any therapy, as reported by Hubbard.¹ This author did point out that "digitalis or one of the digitalis preparations, when given in adequate amounts . . . has invariably been effective in stopping the tachycardia." This was true of eight of the nine cases reported by him, as well as of six of the nineteen cases reviewed by him. The case of Wegman and Egbert, which did not respond to digitalis, was found at autopsy to have rhabdomyosarcoma of the conducting system. Patients in five of the cases reviewed by Hubbard recovered without digitalis, and one of his own patients recovered spontaneously. He states that quinidine is of no value in paroxysmal tachycardia of early infancy; he also reported an extremely severe reaction in Case 6 of his series, in which mecholyl chloride was used.

Our experience bears out to some extent Hubbard's observations. It may be that if the difference between paroxysmal tachycardia of infants and that observed in adults had been appreciated when Case 1 was observed, that digitalis rather than quinine would have been employed, and a more favorable result obtained.

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*Prepared and interpreted by Dr. John Walker Moore.

LEINER'S DISEASE FOLLOWED BY THE CELIAC SYNDROME

A CASE REPORT

H. E. THELANDER, M.D.

SAN FRANCISCO, CALIF.

SINCE attention again has been directed to the condition known as erythrodermia desquamativa (Leiner's disease) in infants, by Glaser and Markson,¹ it seems an opportune time to report the interesting occurrence of the celiac syndrome following recovery from Leiner's disease in my previously reported case.²

In a review of the literature on Leiner's disease, no other case with this combination of pathology was found. and in Andersen's³ article with its comprehensive review of cystic fibrosis of the pancreas and celiac disease there is no reference to any cases associated with Leiner's disease. Even a single instance, however, may add some pertinent piece in the mosaic of information that is being pieced together to complete the picture of Leiner's disease.

CASE REPORT

(Continued from previous article²)

A. B. at the time of the 1937 report was 8 months of age and weighed 18 pounds. Her hemoglobin, which had been as low as 46 per cent, was 70 per cent. Her skin and hair were normal, and she was on the regular diet for her age with the addition of synthetic vitamin C and iron, the former because of a tendency to orange allergy and the latter because of anemia.

Shortly after the original report, the child was taken out of town for a family holiday. Heat and dust storms were encountered and the child developed anorexia which was followed by a persistent diarrhea, refractory to ordinary palliative measures. Upon return from this trip, the patient weighed 14 pounds, 12 ounces, which represented a loss of $3\frac{1}{2}$ pounds in one month. She presented a picture of extreme emaciation and dehydration but was afebrile and had no localized pathology. After a short period of observation, a tentative diagnosis of celiac disease was made; this was confirmed by subsequent stool studies, the clinical picture, and the course of the illness. She was given one transfusion of 100 c.c. whole blood and placed on a celiac regime.

From June 25, 1937, to Dec. 17, 1937, a period of six months, her weight remained practically stationary varying a few ounces up or down at each weighing. She was irritable, wakeful, and extremely unhappy. The stools were characteristically light-colored, foamy, and voluminous. She was emaciated with a large distended, doughy abdomen, flat, sagging buttocks, and slender, fragile looking legs. Her hair was very fine in texture, scant, and slow growing.

Her diet, which at first consisted of peptonized skim milk, bananas, and concentrated vitamins C, A and D, and the B complex, was gradually increased as her stools and general condition warranted it. The additions were made in the following order: cottage cheese made from skim milk, scraped beef, Jello, and gelatin, egg white; these were followed by the cautious addition of selected puréed fruits, and vegetables and, lastly, by carbohydrates and fats. Honey was tolerated better than other sugars and starches. The vitamin B preparations of 1937 were not as palatable as the present ones, but the mother was so convinced that the child was better when taking them that in spite of difficulties of administration, they were given regularly.



When examined on Jan. 10, 1938, the patient showed her first satisfactory gain and general improvement. This change had been preceded by a change for the better in disposition and general comfort, as well as in the character of the stools. From this time on she showed a consistent improvement which is unusual in this condition and can undoubtedly be attributed to the splendid and intelligent cooperation of the parents. The mother prepared every meal and with very few exceptions was present for the feeding. The child was guarded against infection with an almost superhuman diligence.

In 1938, at the age of 21 months, the patient weighed 24 pounds, 5 ounces, a gain of 8 pounds, 12 ounces in six months. Her appearance had improved markedly although her abdomen remained distended. She required careful watching of her diet as even a slight variation would precipitate a return of the irritable disposition, discomfort, and abnormal stools. It was probably because the mother never ignored these warning signs that the child at no time had a true relapse following the initial disease, a rather remarkable fact.

In June, 1939, two years after onset, A. B. weighed 34 pounds and was 37 inches tall. In 1940, at the age of 3 years, 6 months, she was still taking four bananas daily, skim milk, scraped beef, egg in limited quantities, carefully selected and prepared fruits and vegetables, a very restricted amount of butter, and the vitamins C, A and D, and the B complex.

In June, 1941, her weight was 44½ pounds; her height, 44½ inches; and her width, 18 cm., which compared favorably with the normal. Her teeth had erupted normally and were normal in appearance. She had had the routine immunization procedures, she had had an occasional cold, all of which she took in stride. Her diet was still limited in carbohydrates and fats and she showed discomfort when Vitamin B was omitted from her daily diet.

When 5 years of age the family left the city and I have not seen the patient since. A report from the parents in 1944, when the girl was 8 years of age, stated that she was tall and slender but in excellent health, she was doing well at school, and she was on a normal diet with only slight precaution taken in the use of fats and carbohydrates.

COMMENTS

This case is reported because of the occurrence in the same patient in rapid sequence of two poorly understood syndromes. Although I fully appreciate that this may be mere coincidence, nevertheless, there are a few pertinent facts that deserve cognizance. Among the many therapeutic measures suggested by various authors for Leiner's disease is that of a diet low in carbohydrates and fats; Glaser reports pathologic findings in the liver and pancreas in his cases; and the present knowledge of the relationship between deficiencies, causal or resultant pathology, intestinal and skin conditions is meager.

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American Academy of Pediatrics

Proceedings

Meeting of Members of Study Group and Committee on Study of Child-Health Services

A meeting of the members of the Study Group and the Committee on Study of Child-Health Services of the American Academy of Pediatrics was held at the Palmer House, Chicago, on Oct. 20, 1945. There were present Drs. Warren R. Sisson, Joseph S. Wall, Borden Veeder, Joseph I. Linde, Allan M. Butler, Edgar E. Martmer, Clifford G. Grulee, Henry Helmholz, Lee Forrest Hill, Harvey F. Garrison, Katherine Bain, James L. Wilson, Charles L. Williams, Jr., Joseph Lachman, and Mr. Rollo Britten of the U. S. Public Health Service, and Mrs. Elizabeth E. Boles of the Hospital Commission.

The following subjects were discussed at the two sessions which lasted from 9 A.M. to 4:30 P.M.:

Educational Study

Finances of the study, including visitations to various Foundations

Selection of an executive secretary or director of the study, representing the American Academy of Pediatrics

Presentation of proposed schedules by Drs. Bain and Williams of the Technical Staff

Cooperation of the Hospital Commission with the Academy study

Report of the plans for the pilot study in North Carolina, under the direction of Dr.

Lachman, who has been working in the public health service in Kentucky

Report of the visit by Drs. Bain and Sisson to Roaring Gap to meet the members of the North Carolina Pediatric Society

General discussion of the study in reference to pending federal legislation

Selection of a qualified person to cover the so-called public relations activities of the study

Presentation of the committee's activities to the Academy at the meeting in Detroit

Dr. Wilson presented a detailed preliminary schedule for the educational study. He defined the purpose and scope of the study as follows: "To get detailed and, as far as possible, comparable information as to what is taught regarding normal physical and mental development and the illnesses of children in each of the medical schools in the country, this to relate specifically to: (1) undergraduate instruction; (2) graduate instruction. (This may be covered adequately by the hospital intern and resident survey.) Scope: We will define the teaching of pediatrics to include all the information that a pediatrician acting as the family doctor would need to know about infants and children. The survey would, therefore, collect information about the teaching of surgical, otolaryngological, ophthalmological, orthopedic, etc., conditions in children, although not the most technical part of the treatment." Two possibilities for carrying out the study were outlined by Dr. Wilson as follows: "1. A full-time man to take two years to visit personally every medical school. 2. The division of the 70 odd medical schools into, let us say, 7 groups and a crew of 7 men appointed, each to visit one group within a year. The first arrangement is simpler and would give us a more unified basis for comparable opinions and would centralize the clinical work, but has the disadvantage of almost necessarily requiring the time of either a retired teacher of pediatrics or a young man not of national reputation. The second arrangement seems more practical but certainly might result in ten different base lines on which to compare schools. This might be partially offset by careful final summary." Dr. Helmholz

made the following comment concerning the proposed educational study: "I think the thing that we want to emphasize is the education of the men in the medical schools. We as a group of pediatricians would want to think of the education of the pediatrician. In our whole program what we are trying to do is to try to raise the level of what the general practitioner knows about pediatrics. I think we have to emphasize that part of pediatric education not the education of pediatricians, which after all we have pretty well taken care of. There are good schools, better schools, and very poor schools with regard to the actual training of pediatricians. Here we are further raising the level of all men who are practicing medicine. Then I think the relationship of the budget to the course given is pretty much stating in another way what you have said that one institution can give two hundred hours and another cannot give seventy-five because they have not the wherewithal to do it. Along that line we might be able to say what is needed, certain essentials that we cannot get along without. We ought to be able to set a minimum which is necessary to give adequate pediatric training to the man who is going out in general practice. That is something that we could do, not to try to level off at any level, but set a certain minimum that we cannot get along without. If a man has an outpatient department, ten or fifteen beds and no newly born service, you know very well how hard he is trying with a budget of \$2,000 and he cannot adequately teach those students."

In regard to the financial aid for the over-all study, preliminary reports were made by Dr. Wall, Dr. Helmholz, and Dr. Sisson. The National Foundation for Infantile Paralysis has been visited and we are now awaiting a further opportunity to present the plans for the Academy study. The Foundation seemed interested and we are hopeful that they will make a grant. The Rockefeller Foundation has also been approached and our request is still under advisement. We have asked the Rockefeller Foundation if they would be interested to give us the advantage of their experience and also their financial help in promoting the educational study under Dr. Wilson's guidance. In this connection, Dr. Wilson pointed out that the most valuable information that will come out of the educational study cannot be put down on paper. "It is the attitude of the teachers that is most important." The Kellogg Foundation has also been approached for funds. The chairman called attention to the fact that we have spent \$835.96 to date and that the assets of the fund are approximately \$15,000.00 which includes the generous check of \$8,000.00 from the Mead Johnson and Company.

It was moved by Dr. Veeder that Drs. Sisson, Wall, and Helmholz be empowered to act as an executive committee in the interim between committee meetings. This motion was seconded and carried.

The chairman then discussed the various individuals who had been proposed and interviewed as possible candidates for the position of director of the study. It was the unanimous consensus of the group that Colonel John P. Hubbard be invited to take the position and Dr. Helmholz was instructed to send him a telegram to this effect. The meeting was then turned over to the discussion of the various schedules. In order to give an idea of the extent of this phase of the study, the following outline of schedules is listed:

- I. Hospitals, sanatoriums, and related institutions
 - Pediatric hospitals, general hospitals and other hospitals with maternity facilities
 - Special hospitals admitting children: nervous and mental hospitals, and institutions for the feeble-minded; tuberculosis hospitals, sanatoriums and preventorium; convalescent hospitals, contagious hospitals, orthopedic hospitals
- II. Health Services available on a county or city basis:
 - Child health conferences; school health services; mental hygiene services; public health nursing services
- III. Personnel engaged in private practice.
 - Physicians other than pediatricians; pediatricians; dentists
- IV. Training facilities in pediatrics
 - Pediatric departments in medical schools; postgraduate training for doctors; postgraduate training for nurses

Mrs. Elizabeth E. Boles of the Hospital Commission was present at the meeting and gave valuable suggestions in regard to how we could take advantage of the schedules now being used by them.

It should be stated that Mr. Britten of the U. S. Public Health Service made constant suggestions from his vast experience in statistical investigations which added greatly to the discussion.

The chairman gave a brief report of his visit with Dr. Bain to Roaring Gap, N. C., to meet the pediatricians at their annual medical meeting on September 8. The North Carolina pediatricians were most hospitable and we left with the feeling that Dr. London, the President of the Society, would be unquestionably successful in engaging the complete cooperation of the pediatricians of the state.

Dr. Lachman then presented in detail the plans for carrying out the pilot study in North Carolina. The time schedule which Dr. Lachman has developed for this study should bring the work to a successful conclusion by the middle of December. Dr. Lachman pointed out that he felt he could, by personal visitations to the pediatricians, make it clear that our study is not a part of the Pepper bill, which seemed to be a prevalent opinion in certain parts of the country. He emphasized that the purpose of the study is to discover the extent of medical facilities in order that physicians may adapt them to their local needs. At this point, Dr. Butler made a similar remark: "I do not see why we cannot emphasize that this is a study by doctors for doctors that will bring to doctors the information they need to carry on their work."

The committee next discussed the possibility of obtaining the services of a person qualified to present the plans and activities of the committee to the medical profession and to the public at large. Dr. Veeder emphasized the willingness of the editors of the JOURNAL OF PEDIATRICS to include reports and editorial comments concerning the committee's proceedings. It was the conclusion of the group that we should be very careful in the selection of the person for the position of public relations and it was resolved that the matter should be given more consideration before final action was taken. In connection with the question of publicity, it seemed very desirable to the committee to have an opportunity to present the agenda of the Committee on Study of Child-Health Services at the Detroit meeting of the Academy.

The committee decided to reconvene at the time of the Academy meeting in Detroit.

Academy News

The deaths of the following Fellows have been reported to the JOURNAL:

Dr. Robert G. McAliley of Atlanta, Ga., at the Walter Reed Hospital, Sept. 15, 1945.

Dr. Archibald D. Smith, Garden City, New York, Nov. 23, 1945 (Emeritus Fellow).

Dr. Manning C. Field, Brooklyn, N. Y.

V The Social Aspects of Medicine

Suggestions for the discussion on social planning at the approaching Academy meeting in January:

1. Let us not waste time saying that physicians are superior ethically to other occupational groups. Physicians by and large probably do not differ much from the general run of human beings. It is much safer for us to assume that anyway.

2. Let us not waste time, either, in saying how enlightened pediatricians are. The pediatricians have been most forward in the practice of preventive medicine, but that development was a corollary to our work and need not go to our heads.

3. Also let us not waste time in pointing to achievements in medicine of the last twenty years as if they implied that the public need have no voice in determining medical care. The achievements in medicine merely parallel those in chemistry, physics, and mathematics; they are just part of a general advance in science. The essential point is that the advances in medicine have far outstripped their social applications and have created new needs and possibilities.

4. In our discussions let us keep ever in mind that both sides are actuated by a common desire to make medical care adequate. One side is approaching the problem from the point of view of the recipient and tends to see things in a Utopian luster and perhaps does not think enough in terms of practicalities. The other, approaching the problem from the point of view of the purveyor of medical care, tends to think too much in terms of administrative technique and perchance does not see in large enough perspective the objects to be gained. There should be no ground for emotion. The differences are just differences of judgment.

5. In all our discussions let us think primarily what is best for the children and, no matter what comes up, never lose sight of that goal. Physicians are the providers and ministers of medical care. Proposals for improved care are not designed for their comfort or emolument but for the comfort and welfare of the people. The great mistake which some medical groups are making is to think primarily of themselves, as if the medical profession formed a great trade union and the important thing was not to give up any advantage or to make any change until forced by pressure. Let us not allow our own images to obscure our view.

6. Whatever we do at the approaching meeting, let us offer something constructive and not commit the error of tearing to pieces plans for improved medical care without proposing any alternative beyond the preservation of the status quo. If any one single fact is clear, it is that the status quo is not enough to satisfy the public demand. Further, not only must we develop constructive proposals, but they must be sounder and better than others so that they will be accepted on their inherent merits. Proposing something wiser and better than the present bills offer is the only way by which these bills or their children or cousins can be defeated. The President in his recent message to Congress mentioned among the "certain rights which ought to be assured to every American citizen" "the right to adequate medical care and the opportunities to achieve and enjoy good health." Any recommendation endorsed by the Academy of Pediatrics must be big enough to have that end in view.

7. In our thinking and recommendations let us not hesitate to strike out for ourselves. There is a great opportunity at the present time for medical leadership and leadership can only be accomplished by independent thought and action. The present opening for wise action is the greatest that pediatricians have ever had.

E. A. PARK.

COMMUNICATIONS

December 7, 1945.

In the early fall Dr. Harold Root of Waterbury, Connecticut, wrote me a letter for my column. Being a good friend of Dr. Root I took the liberty of criticizing it. Root wrote a vigorous defense of his position. I liked his letter of defense so much better than the original that I am publishing it. The original letter was a formal statement; the latter has all the advantages of informality, spontaneity, and directness and gives the clearer view of the thinking of the author.

E. A. PARK.

103 North Main St.,
Waterbury 14, Conn.Dr. Edwards A. Park,
The Johns Hopkins Hospital,
Baltimore 5, Maryland

Dear Dr. Park:

I was very much interested and a little disappointed in your letter of November seventh. My experience has been that the majority of full-time physicians in teaching medical centers are in sympathy with government control of medicine; and I did not expect that our ideas on this subject would be identical.

We are all in agreement on one thing, good medical care at reasonable cost for all individuals, the question of method is where we differ.

The rank and file of doctors who do the hard work, night calls, treatment in the homes under anything but ideal conditions, the grueling twenty-four hour a day seven days a week on call sort of a job, are unfortunately not all idealists and do not always do exactly the right thing at the right time. They do, however, do a fairly efficient job in the majority of instances. It is the ones who do not do such a good job and cannot make a decent living, who lower the standards of care in any plan, and who gravitate into the Armed Services and particularly the Veterans Administration. I know several in Waterbury and Connecticut who did so after the last war and others who are headed that way now. This is not so apt to be true in the State and Public Health Services. Most of the applications are from this type person, but they are well screened before getting the job. I have served on the Connecticut examining board, and know.

Do you know who goes to the refresher courses, clinical congresses, and educational medical gatherings? Usually the same old crowd, those physicians who need the instruction least, but are determined to keep up as best they can with the newer developments. I am afraid that under government direction with fixed salaries, and fixed routine with the competitive factor removed, the desire to do the best work and to keep up with the latest advances might be further retarded.

This is demonstrated by any number of instances which I can quote you from personal knowledge of working conditions in the Army. The reluctance of the medical officers to do anything out of the ordinary routine or after hours for even the alleviation of the sick. Of course I am speaking of the rank and file, not the higher type medical officer. The rank and file are the ones who will bear the burden of any government program, however. This type person is also the one who doesn't care to take the trouble to keep abreast of the times.

Another type of government inefficiency: Two hospitals in England twenty-five miles apart. One of a certain type calling for a comparatively small staff, the other a different type calling for a larger staff. The smaller hospital consistently gets at least twice as many war casualties as the larger. The staff here works almost continuously trying to

keep up with the rush, whereas the staff in the larger hospital sits around a great deal of the time. Can anything be done to correct this? No, according to the Army officials. Rules are rules and the staffs must do the best they can under the circumstances. This is the type of inefficiency I am afraid of under government control.

Many of us attend well child conferences run by the city or State. In a discussion with some of the best pediatricians in the State a short time ago, we were all regretting that we could not do as good work at these conferences as in our offices due to the fact that we have to see so many patients in such a short time. This condition, I think you will find, applies in most, if not all, such clinics. You may say this is better than nothing. True, but not better if made nationwide under government control than facilities such as well child conferences, maternal clinics, dispensaries, T. B. clinics, etc., etc., that are now available to everyone in the States with good health programs. Those States without good programs should of course have facilities provided, as they will be under the Hill-Burton bill which is receiving the backing of organized medicine. My point is that where need has been demonstrated, the States should expand the existing services to meet those needs with government assistance where necessary.

For instance the Pepper bill calls for care of all mothers, regardless of race, creed, or financial status, all children under twenty-one, all crippled children, etc., etc., and yet appropriates only \$100,000,000.00 for this program. Why not see what needs are demonstrated in the survey of the postwar planning committee of the Academy of Pediatrics and then propose legislation to meet those needs?

I will attempt to answer your criticisms point by point.

1. My reason for listing some of the accomplishments of medicine up to the present time was to show that a great deal has been and is being accomplished without government control of medicine. There was no implication of perfection. Just a record to be proud of. Perhaps it should be omitted.

2. There is a panel system in England, Australia, New Zealand, Canada, and most of the other government managed plans. The plan in England is admittedly unsatisfactory by all parties, government, doctors, and people. The British Medical Society has several times endorsed the plan in the past twenty years, but always suggests improvements, and points out the weaknesses in the plan. There has been little improvement since 1911. Thus far, hospitalization has not been included, nor specialist services, nor care of dependents. The doctors are allowed an unlimited number of patients on their panels which leads to rush medicine, and poor care.

In New Zealand the plan is more inclusive. It started on a fee per panel patient per year basis. The fee was small and the patients demanding in their care. The doctors were very dissatisfied. A change was made to fee per visit, then to a plan where the patient paid part of the fee. The paper work and dissatisfaction of both doctor and patient has mounted steadily particularly recently, and the government has not enough appropriation to meet the cost. The plan is, therefore, near collapse. The care of natives is not included in the plan. There is no provision for the indigent in either of these plans.

In Sweden there is a very satisfactory government plan, government owned hospitals, etc. Nearly all costs paid by the government, not an insurance system.

In Norway and Denmark with a homogeneous type population a satisfactory compulsory insurance system had been worked out. Almost complete medical, dental, and hospital care. It is interesting to note that the individual pays 0.6 of the fee for medical care, government 0.1, employer 0.3.

3. My letter was written to express some reasons why I feel that the lay person would not get as good medical care at reasonable cost under the Murray-Wagner-Dingell bill as by the combination of voluntary prepaid medical plans, plus hospital insurance plans plus expansion of State Health Department Services as need is demonstrated with government assistance where needed, plus plans for care of the indigent by the community or State again with government assistance where needed.

There are already 18,800,000 members of the prepayment hospital plans and it is only beginning in some states. Connecticut has well over one-fourth of its population enrolled in this plan and it is growing rapidly each month. Prepaid medical plans are just starting in most states and will undoubtedly help solve the problem of good reasonable medical care.

I realize that doctors are servants of the public, perhaps even better than you, and that the majority of the people will get what they want or think they want. Having corresponded at some length with the editor of the C.I.O. periodical in this area, I also know something of its goal as to medical care and sympathize with it.

Medical care in some States, notably in Connecticut, is rather efficient and becoming more so all the time as the State and other health programs develop according to need. There are large areas where there are no doctors. Are you or am I going to these areas if government takes control? Who, even though subsidized, is going to these thinly populated areas where practice is so spotty?

There is a very efficient mechanism in many communities whereby the indigent get good medical care of which I could tell you the details. Of course in others there is none. What about Maryland's new plan as published in the October JOURNAL OF PEDIATRICS? What about many other plans in the developmental stage? Would it be any better under governmental control with the usual red tape involved? Good dental care for all children would be ideal and I am all for it. Many States are developing or have developed excellent dental programs. Here again by all means government aid to the States who need assistance to attain this goal. The same applies to medical centers where needed. I sincerely hope the medical schools can and will take over the task of keeping up the education of the doctors in a community, but how are you going to get the doctors, rank and file, to go and be educated?

My letter may be destructive as far as the Murray-Wagner-Dingell bill is concerned, but did you notice the program which I suggested on the last page of my letter and have repeated in this letter? I grant that doctors have been slow to awake and even slower to propose cures for the medical ills of the world. I know that hundreds of them now are devoting a great deal of time to the study of this question and are trying to work out a solution which will react more to the benefit of the public than government control. Some of us still think this can be done. I believe that the government should set standards for care and see that they are carried out by the States with financial assistance by the government where needed.

We may both be wrong, but at least we are thinking toward the same ends.

Sincerely yours,

J. HAROLD ROOT, M.D.

November 15, 1945

November 27, 1945

Honorable Claude Pepper, Chairman
Subcommittee on Wartime Health and Education
Committee on Education and Labor
United States Senate
Washington, D. C.

Sir:

I have your letter of October 24, 1945, inviting me to comment on your bill S-1318 concerning maternal and child welfare in this country. I am taking your invitation literally. I write as a professional teacher of pediatrics and as one who receives a very minor part of his income from private practice.

The purpose of the bill and the ends desired to be reached, seem to me so admirable as to need no defense or comment. Any differences of opinion must be about a means to these ends.

I do not believe that the present members of the medical profession would be able to do as good a job as they are now doing if bill S-1318 were put into effect with no more controls on the rate of its actual implementation than are now provided. The bill as written, like other bills I have seen and particularly the all-inclusive Murray-Wagner-Dingell bill, is based on an idea which seems almost naive to an actual practitioner of medicine as myself, that is, that most of the troubles of mind and body that we see so pathetically prevalent in our children are due to such lack of financial resources by parents that they are unable to pay for proper medical and hospital care. Regardless of how much money is appropriated by Congress or State legislators or by philanthropic organizations, it can be said without qualification that the sort of medical care given to our people in the next twenty years is being determined now by what is being done in our medical schools and in graduate teaching hospitals.

A general tax supported medical payment scheme would certainly enable some children to get medical care that otherwise they would not receive. It seems to me, however, that there is far too great emphasis on this aspect of the problem and that a vastly greater part of the difficulties that result in the physical and mental defects of children are due to more profound and important factors which are open to direct solution and that steps toward their solution should be taken before a medical prepayment project on a national basis is undertaken.

One of these fundamental difficulties is the obvious one that the science of medicine has not progressed to the point where much effectively can be done about a great many of the ills and complaints to which man is subject, such as many of the most striking ones obvious to the man in the street, as arthritis and paralysis. This, of course, is in itself no argument against your proposals as one should make full use of what medical knowledge exists at present, but it is important for proper orientation in comparing what could be accomplished by a great extension of the present habits of medical practice, as would be accomplished by effects of bill S-1318, versus research to directly attack the basic defects in medical knowledge. Another problem that must be clearly analyzed is that states of nutrition and physical environment dependent upon intelligence and economic status have great bearing on health, so much so that the figures that you quote in your speech introducing the Pepper bill when you compare the infant mortality of Connecticut and New Mexico reflect the influence of a great many more factors than the amount of medical services available in the two states.

Any critical and sophisticated observer of the actual practice of medicine would agree with me that by far the greatest obstruction in the path to universal good health of children, in addition to the fundamental lack of medical knowledge which can be met only by medical research, is a great shortage of doctors, a great defect in the distribution of doctors, and, most important, a great defect in the quality and training of the doctors that we do have. These difficulties are immeasurably more important than lack of funds to pay for medical care. In my opinion a large proportion of the practicing physicians in this country are unable to wisely or skillfully diagnose and care for ailing infants, so that in many instances their attention can and does result in more harm than good. The crying need in this country is for more doctors and for better doctors, skilled in the care of infants and children. Undoubtedly the same thing can be said in other fields of medicine. In this bill there is a brief, almost casual mention of research and education. No clear-cut program is proposed, or precise allocation of funds made for these purposes. No assurance seems given that even the vague suggestions made regarding aid to education and research would be adequately carried out by state organizations who may be more interested in giving direct aid to individual voters. The total of the budgets of all the medical schools in this country is now less than forty million dollars, an amount trivial compared to that proposed to be appropriated for the purposes of bill S-1318. During one twelve month period the cost of the EMIC program alone, a program offered by the government without proof of need, as a gracious and justified gratuity to the members of our Armed Forces,

was about one and one-half times as great as the total budgets of all the medical schools in the country. Graduate education, by which I mean training of physicians as interns and residents after receiving their M.D. degree, is pathetically inadequate. Only a small proportion of the hospitals in this country are suitable for such training. The demand for good training opportunities was immensely greater than the supply even before the great aggravation of this difficulty by the return of medical veterans from the war. It seems to me therefore, almost absurd to indulge in this great preoccupation with techniques of distribution of medical care rather than to concentrate on the improvement of the quality and quantity of physicians. The future of medical research as well as medical education is entirely bound up in the facilities and ideals of our medical schools, yet most schools are operated on financial shoestrings with inadequate staffs and with research supported by temporary gratuities from drug companies or by foundations who want to initiate studies from which acknowledging papers can be made in one or two years.

The success or failure of the program outlined in the bill in meeting the desirable ends will obviously depend to a great extent on details of administration. All these are left for decision, apparently at the state level. It seems to me that unless many of these details can be boldly and courageously faced by Congress before being passed on to the state, it is obvious that enormous difficulties will rapidly arise about such a widely sweeping project, difficulties which will soon end in confusion and acrimonious arguments and strife between public health administrators and the medical profession. This might easily be tolerated if we were sure that the final results achieved would be good. It would seem that an almost inevitable leveling of fees to physicians would take place, in itself unimportant unless it resulted, as I strongly believe it would, in a failure of stimulation of the better trained practitioners and encouragement for the rapid production of the more poorly trained practitioner. In the last fifteen years there has been a rapid increase in the number of men practicing the specialty of pediatrics. These physicians spend a minimum of two years in a pediatric training center and then devote themselves wholly to practice limited to infants and children. In the last decade and a half they have decidedly raised the type of medical care that the children in this country receive. Although at present they do not care for more than 10 per cent of our child population, the number of such men training themselves for certification by their Board was increasing year by year at a rapidly accelerating rate up to the time of the curtailment of all such training by the war. You should understand that these men practiced their "specialty" not in a consultative capacity for wealthy and especially puzzling patients, but much more as general practitioners particularly trained to give continuous and complete care to their young patients. The use of these men, therefore, in a position only as consultants with a fee devised for that purpose is in no way in line with the natural and gratifying development of pediatrics. Such schemes as a national insurance plan, adopted at this time with such a small proportion of men with special training available would greatly handicap the development of more pediatricians unless a special fee for them could be devised, and such an arrangement would be indeed extremely difficult to administer as it has proved in other less extensive programs. Almost the same obstruction would arise to the development of more trained obstetricians, not to be used only in matters of emergency or consultation, but for the routine care of the average woman. Unless far more particularized organization of the administration of the bill were planned than appears at present, and unless some of the most controversial problems of medical economics are first solved in a manner that I am not wise enough myself to plan, I firmly believe that the fine purposes of the bill will be defeated by a nationwide increase in the quantity with great decrease in the quality of medical care given. I do not believe the public, and much less the medical profession, is yet able, or will be in the next few years, to use wisely the enormous funds that would be so soon available without such waste as to soon disgust our voters. Although certain states with population in the lowest economic group might attract more needed physicians, it seems to me there is little provision in the bill for means to attract the best trained instead of the worst trained practitioners.

A detail of the bill relatively unimportant might still be mentioned. S-1318 makes a distinction between sick children and crippled children. This distinction is common in state as well as national medical service programs and seems to be carried along in the legislative mind with little reason. The classification seems to me highly artificial since no one knows exactly what a "crippled" child is. Attempts to make such distinction causes over-emphasis on the sort of crippling that can be seen by casual lay observation and brings about great and unnecessary confusion in administration. I think any program for improving the general medical welfare of children should avoid distinctions between the anatomical localization of their infirmities. Programs which separate a child's psyche from his body, his heart from his lungs, and a paralyzed leg from nutritional defects, are, in my opinion, fundamentally illogical and lead to dangerous habits of medical thinking although they do appeal to groups of workers with special and limited interests.

The broad criticisms of the bill that I have been so bold to make should not imply that I think the Federal government should not engage in activities to improve medical care. Even with the present limits of the science of medicine, there is a wide gap between what is known and what is generally applied. Instead, however, of a project attempting blindly with one sweep to wipe out medical indigence in the way so naively attractive to the medical laity, I believe legislation carefully worked out to attack first a variety of underlying problems should be devised. Legislation should be planned to stimulate improvement in medical knowledge, in medical education, and in distribution of physicians and health workers as a primary object, and not leave these all-important matters as secondary projects to be casually acted upon by state legislators more interested in the distribution of high sums for direct medical aid to individual voters. It seems to me, therefore, that the approach toward solving the fine ends described as the purpose of this bill must be made first by specific attacks on the problem of education and training.

Congress should provide facilities for direct financial aid to first class medical schools now existing and for others to be formed and make such aid provisional to the maintenance of standards set by the entire group of medical schools themselves.

Congress should give direct aid to medical research and not only by setting up new agencies for specific projects but by broad grants to existing institutions. Medical education and research cannot be separated. The total amount spent for medical education and research should be multiplied many times.

There is great need for a large Federal fund to improve the distribution of medical care by contributing to individual and different programs the country over. Grants should be made for furthering the development of different schemes for improving medical practice where local organizations or communities desire it and can offer an intelligent plan. Federal aid for support of local prepayment or health insurance plans should be widely given, obviously along with some control of the scheme.

Not only should more hospitals be constructed, but far more important, support of teaching within those hospitals should be specifically made. Money for the support of resident physicians in many hospitals would often do far more good in improving medical care than direct financial aid to the patients.

Subsidies to physicians by country communities has often been successful in extending medical care to places where it is deficient, and such schemes should be given government support to attract physicians to communities where they seem to be most needed.

There are wonderful possibilities for improving the care of patients in the decentralization and extension of graduate medical education to small outlying hospitals to which the fostering and stimulating influences of a medical school could be extended. Many more good young physicians would spend five years in hospital training if they could be financially supported and if more teaching hospitals existed.

A great deal of experimentation in methods for reduction of the cost of medical care needs to be carried out. Subsidies for aid in the establishment of group clinics could quite properly be made as long as some control was made over the financial arrangements so that

the grants could not be exploited for the benefit of the physicians. Group clinics can be organized to give the finest medical care at greatly reduced costs. Where available, medical schools could logically be the focal point for organized group practice programs.

The functions of the present Children's Bureau which has accomplished so much should be greatly broadened and coordinated with other government departments concerned with public health. The identity of the Children's Bureau should not be lost but its place is obviously not in the Department of Labor. Its proper and logical function in carrying on problems of research, particularly those of necessarily national scope, have been almost completely ignored by Congress. It already has accomplished much in general education and could and should do far more. It is the obvious Federal agency to carry on the projects I have suggested as they relate to maternal and child care. The use of the Children's Bureau as an agency to direct the distribution of local medical care to individual patients seems very likely to diminish its effectiveness in more important fields.

Sincerely yours,

JAMES L. WILSON, M.D.

Brookline, Mass.

December 6, 1945

Dear Dr. Park:

As requested, I am sending you my conception of what the Pepper bill (S. 1318) would mean to the pediatrician now actively engaged in private practice should the bill be enacted into law.

To maintain the proper perspective we pediatricians must recognize: (1) that the objective of the Pepper bill is to provide medical care for over 40,000,000 "children" and, (2) that there are at this time 2,354 certified pediatricians in this country—a ratio of one certified pediatrician to 17,000 "children."

The actual medical care for the vast majority of children under the Pepper bill will be given by the family physician. This is the situation as it exists now and as it will continue for many years to come until a sufficient number of pediatricians are trained to assume the task.

The pediatrician has an important role in the successful operation of the Pepper bill, but this role is *not* to enter into competition with the family physician by offering to give medical care on the *per capita* basis.

The trained pediatrician can best serve the public and himself under the Pepper bill by rendering service at the consultant or specialist level. Since there will be too few certified pediatricians to fill the needs of the program even at this level, it is probable that, as in the EMIC program, a consultant will be defined as one who is a consultant in his specialty on the active staff of an approved hospital.

It is probable that many men in private pediatrics will continue to give service in well-baby clinics, well-child clinics, and out-patient departments as well as through visiting on hospital wards. These services under the Pepper bill will be paid for on a *per session* basis. We have no way of knowing what this remuneration will amount to, but we do know that the bill insists on a high quality of medical care through adequate remuneration. The individual state's health agency will determine these fees after consultation with the state's professional advisory committee.

If the pediatrician wishes to participate in the program as a consultant, he will receive a consultant's fee only if the attending physician requests the consultation and executes the appropriate forms. We do not know what the fees will be under the Pepper bill, but in the EMIC program in Massachusetts a consultant received for an office visit,

\$5.00; for a hospital visit when the consultant was on the staff, \$5.00; for a home visit or visit to any other hospital, \$10.00; for care of a referred infant during the first two weeks of life, a maximum payment per week for three or more hospital visits, \$6.00. This method of payment constitutes the *fee-for-service system*.

The pediatrician in the program would probably care for many referred patients under the *per case system*. This system would pay the consultant or specialist a stipulated sum for the total service he would render a patient during a particular illness or because of a particular condition, usually within a stipulated period of time. We have no means of knowing what the schedule of fees for various types of cases will be. We do have the assurance that the remuneration will be adequate as determined by a professional advisory committee.

A group of pediatricians might contract with the state health agency to provide medical care as consultants, or one or more pediatricians may contract to give postgraduate teaching, and the *salary system* might, under certain conditions, be a desirable method of paying for such medical services.

The present draft of the Pepper bill provides medical service to *all* without a means test. If the present bill should become law we are naturally concerned as to what will become of the pediatricians' private practice. I do not know the answer to this important question, but I do not think that many of our patients who can afford otherwise will accept any but the highest type of service for their children, and I doubt if they would accept hospitalization for their children at the ward level with all that that implies.

I do not see how the bill could be passed without some reasonable means test being applied by the individual states. If this should prove to be the case I do not believe the operation of the bill would injure the private practice of pediatrics.

In summary, I believe the pediatric specialist under the Pepper bill should serve at the consultant or specialist level only. I do not believe the bill would diminish the demand for private pediatric care by those who can afford to pay—particularly if a means test is included. The private pediatrician would continue to work in clinics and outpatient departments and on the hospital wards as he does now—the only difference being that he would have the novel experience of being paid for his services instead of giving them free.

Yours very sincerely,

STEWART H. CLIFFORD, M.D.

News and Notes

Dr. Milton J. E. Senn will deliver the fourteenth annual series of the Benjamin Knox Rachford Lectureships in Cincinnati on Tuesday evening, February 5, and on Wednesday evening, February 6, 1946, at 8:15 P.M. in the auditorium of the Children's Hospital Clinic and Research Building. The subjects of his lectures will be "The Relationship of Pediatrics and Psychiatry" and "Opportunities for Psychotherapy in Pediatric Practice."

Dr. Hart E. Van Riper, formerly with the Children's Bureau and later at the Jackson Memorial Hospital in Miami, Fla., has been appointed Assistant Medical Director of the National Foundation for Infantile Paralysis, Inc.

The Pediatrician and the War

The following promotions have been reported to the JOURNAL:

Army

Major J. Hugh Lewis, Wyandotte, Mich., to Lieutenant Colonel
Major Oscar B. Markey, Cleveland, Ohio, to Lieutenant Colonel
Captain William B. Nevins, East Orange, N. J., to Major
Major A. W. Pinkerton, Lima, Ohio, to Lieutenant Colonel

Navy

Lieutenant Commander Howard J. Morrison, Savannah, Ga., to Commander
Lieutenant Commander Morris Steiner, Brooklyn, N. Y., to Commander
Lieutenant Commander James H. Wallace, Oak Park, Ill., to Commander

The following Fellows have been released from military service:

Dr. Arthur F. Abt, Chicago, Ill.
Dr. Bernard Benjamin, Brooklyn, N. Y.
Dr. Montgomery Blair, Jr., Washington, D. C.
Dr. John B. Burns, Binghamton, N. Y.
Dr. Edwin R. Cole, Sacramento, Calif.
Dr. Wyman C. Cole, Detroit, Mich.
Dr. Richard G. Elliott, Lexington, Ky.
Dr. Ernest Freshman, Oneida, N. Y.
Dr. Paul Herzog, Kenosha, Wis.
Dr. John P. Hubbard, Washington, D. C.
Dr. Herman Landon, Chicago, Ill.
Dr. J. Hugh Lewis, Wyandotte, Mich.
Dr. Gordon Manace, Toronto, Ontario
Dr. Edgar F. Martmer, Detroit, Mich.
Dr. J. Keller Mack, Springfield, Ill.
Dr. Halcuit Moore, Dallas, Texas
Dr. Masters H. Moore, Tyler, Texas
Dr. Robert H. Moore, Dallas, Texas
Dr. Councill C. Rudolph, Coral Gables, Fla.
Dr. Harry Strongin, Brooklyn, N. Y.
Dr. Abraham Tow, New York, N. Y.
Dr. Tyree C. Wyatt, Syracuse, N. Y.

Book Reviews

Virus as Organism. Frank MacFarlane Burnet, Cambridge, Mass., 1945, Harvard University Press, 134 pages. Price \$2.

Dr. Burnet is widely known as an authority on virus diseases and as Director of the Eliza Hall Institute of Research in Pathology and Medicine of Melbourne, Australia. The present book was presented as the Edward K. Dunham Lectures for the Promotion of Medical Sciences at Harvard University in 1944 and deals with the broader aspects of virology and virus disease as well as with certain selected diseases, such as herpes simplex, poliomyelitis, psittacosis, smallpox, yellow fever, and influenza, with special reference to their ecological aspects. The first two chapters deal with reproduction, variation and survival of viruses, and with evolution and change in virus disease. It is interesting to find that Burnet finds it necessary in the case of viruses, as Pasteur did so many years ago, for bacteria to combat the theory of spontaneous generation. The occurrence and importance of heritable mutations in viruses which lead to changes in virulence and severity of epidemics are stressed. Dr. Burnet's comments on the epidemiology of poliomyelitis were of great interest to this reviewer, especially his observations in Melbourne that some fairly direct chain of contact between *children* could nearly always be traced, and that there was no evidence of carriage of infection by adults.

This book will be of value to all who are interested in the clinical and epidemiological problems as well as in the fundamental principles of virus infection. It is not only authoritative, but also very readable.

H. K. F.

Paper in This Issue

Due to conditions beyond the control of the editors and publishers, this issue of the JOURNAL is printed on uncoated paper.

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Original Communications

LIPEMIC NEPHROSIS

WALTER HEYMANN, M.D., AND VIOLA STARTZMAN, M.D.
CLEVELAND, OHIO

THIRTY-FOUR children ill with lipemic nephrosis have been studied during the past twelve years. The survey excludes cases of glomerulonephritis which secondarily developed the nephrotic syndrome, but includes those of primary lipemic nephrosis even though in some instances symptoms of nephritis may have occurred during the later stages of the illness.

The existence of *lipemic nephrosis* as a definite clinical entity has not been unanimously accepted. Most internists believe that the disease is a manifestation of chronic nephritis,¹ whereas the majority of pediatricians are of the opinion that it represents a clinical as well as a pathologic entity.² We share the latter belief and explain the divergence of opinions by the fact that lipemic nephrosis is predominantly a disease of *early* childhood and is very rare or possibly nonexistent in adults. The ultimate decision as to whether lipemic nephrosis is a clinicopathologic entity rests mainly on the pathologic evidence.

Of the ten deaths of children in this series autopsies were performed in six. In three of these six autopsies there was neither gross nor microscopic evidence of inflammatory disease in the kidneys.* In these three cases death occurred early in the course of the disease, i.e., three, five, and six weeks after the onset, respectively. In two, the death was due to the mercurial diuretic salyrgan, and in one to bronchopneumonia. Sections were stained with hematoxylin eosin, azocarmine, and sudan IV. The glomeruli were normal, the basement membranes were not thickened and there was no interstitial infiltration. Because of the fact that the basement membranes were entirely normal, we cannot agree with Bell³ and Fahr¹ who believe that the thickened glomerular basement membrane is the basic and essential lesion in the nephrotic kidney. Our findings are in agreement with those of Kantrowitz and Klemperer^{4a} and

From the Babies and Childrens Hospital, and The Department of Pediatrics Western Reserve University.

Aided by a grant from the John and Mary R. Markle Foundation.

*We are greatly indebted to Dr. H. Goldblatt and Dr. T. C. Laipply of the Institute of Pathology, School of Medicine, Western Reserve University for re-examining the slides and tissues studied.

of Wolbach and Blackfan,^{4b} from which it can be concluded that anatomically lipemic nephrosis is a noninflammatory lesion of the tubular apparatus, often being present without any microscopic evidence of glomerular or interstitial inflammation. The other three children on whom autopsies were performed died from intercurrent infections. One had bronchopneumonia; one, bronchopneumonia following measles; and the other, pneumococcic peritonitis and septicemia, death occurring one and one-half, six, and thirteen months, respectively, after the onset of the renal disease. Histologic examination revealed marked nephrosis and also inflammatory disease. The nephritic lesions in these kidneys were described by Drs. H. Goldblatt and T. C. Laipply as slight, acute pyelonephritis in one instance, as acute, proliferative glomerulonephritis with slight, chronic, interstitial nephritis in the second, and as chronic pyelonephritis with marked fibrosis of the glomeruli in the third. Only in the first of these three cases were the glomerular basement membranes found to be thickened. From the point of view of the pathologists, the diagnosis in these instances is interstitial nephritis rather than glomerulonephritis.

Our clinical observations in twenty-one of our patients coincide with the anatomic picture. Four to eighteen months of uninterrupted observation included daily urinalyses and blood pressure readings and weekly blood chemistry determinations. Fourteen of these children were at all times free of nephritic symptoms. In three others there were some signs of nephritis at the onset, the duration of which varied from ten days to six months. These three children presented from then on the symptomatology of lipemic nephrosis exclusively. In the other four patients, there was a transient episode of nephritis during the late stages of the nephrosis.

Both the anatomic and the clinical observations justify our conclusion that lipemic nephrosis often occurs without the added presence of nephritis, and that it is a clinicopathologic entity, often combined with, but as such unrelated to chronic nephritis.

The *clinical diagnosis of an additional nephritis* in lipemic nephrosis often requires months of study. It is obvious that more than an occasional red blood cell, often observed in a normal centrifuged urine specimen, should not be found in the urine of a patient suffering from nephrosis. We noted, however, that the absence of erythrocyturia for several weeks did not exclude the possibility of the additional existence of nephritis. In one of the three nephritis cases, in which an autopsy was performed, erythrocyturia was absent during six weeks of observation. In one other it had been observed for only four weeks, ten months prior to death. Within the last three months of life this patient's urine was free of red blood cells and yet the microscopic examination of the kidneys revealed pyelonephritis and glomerulonephritis. In the absence of erythrocyturia repeated readings of the blood pressure, nonprotein nitrogen or blood urea nitrogen and creatinine determinations in the blood over extended periods are necessary to solve the diagnostic problem. In cases of additional interstitial nephritis the values may be moderately increased and fluctuate, usually unobserved in uncomplicated glomerulonephritis (Table I). It is our

TABLE I. CASES OF LIPEMIC NEPHROSIS WITH ADDITIONAL NEPHRITIS SHOWING MODERATE INCREASE AND FLUCTUATION OF NONPROTEIN NITROGEN AND CREATININE VALUES

DATE	NAME	AGE IN YEARS	SEVERITY OF NEPHROSIS	URINE SEDIMENT		BLOOD PRESSURE	SERUM MG. PER 100 C.C.		
				R.B.C.	W.B.C.		N.P.N.	U.N.	CREAT- ININE
2-15-43	J. D. G.*	2	4+	+	2+		54	32	1.4
2-16-43				2+	3+		56	40	1.5
2-23-43				0	+		47		
3- 8-43				0	-		28		
3-23-43				0	-		36		1.0
4- 8-43				+	+		45		
4-12-43				2+	+		64		
4-17-43				few	+		47		
4-23-43				2+	+		48		1.9
5- 3-43							72		1.4
5- 7-43							56		1.2
5-10-43				2+	few		40		
5-21-43				2+	few		78		
6- 3-43				2+	few		76		1.5
7- 3-44	R. O.	1½		few	+		30	15	1.2
7-10-44				few	2+		78		
7-17-44				-	few		46		
7-24-44				-	few		33		
7-31-44				-	-	90/40	23		1.2
10-23-36	G. M.	13	2+	+	-	130/90	28		
10-26-36				few	-	130/90	29		
11-30-36				-	few	130/90	42		
12- 7-36				-	few	125/80	47		
10-19-43	B. B.	2	4+	-	-	110/70	36		0.9
10-26-43				-	-	110/70	50		1.1
2-25-44				2+	+	105/90	35		
2-28-44				2+	3+	105/80	33		0.8
3-13-44				-	-	110/75	37		1.0
3-22-44				few	-	95/40	38		1.1
3-27-44					-	90/40	43		
4- 3-44				few	-	90/40	35		1.1
4-10-44				0	-	90/45	36		1.0
4-17-44				0	-	90/55	35		1.0
6-19-44				0	-	90/40	26		
7-10-44				0	-	80/40	55	30	
8- 7-44				0	-	100/45	27		0.8
9-11-44				0	-	90/55	28		0.8
5-20-33	F. B.*	3	3+	-	3+	100/70	29		
7-27-33				-	2+	120/70	63		
8- 5-33				few	2+	100/70	47		
9-11-33				few	+	110/90	69		
8-15-33	H. R.*	2½	3+	+	+		76		
8-24-33				+	2+		92		
9- 5-33				2+	+		46		

*Diagnosis confirmed by microscopic examination of the kidneys.

impression that the fluctuation found in nitrogen retention and creatinine values is quite characteristic for this type of nephritis.

The *etiology* of genuine lipemic nephrosis is unknown and our experience has yielded but little new knowledge. We believe that the disease is not so rare in children as is generally assumed. During the last twelve years 115 cases of glomerulonephritis and 34 of lipemic nephrosis were admitted to Babies and Childrens Hospital, Cleveland. In our hospital population the incidence of glomerulonephritis is consequently only 3.47 times more frequent. One important factor is that the incidence is greatest during the first two to three years

of life. Of the thirty-four cases, twenty-one (64 per cent) were under 3, seven (21 per cent) between 4 and 7 years and five (15 per cent) between 9 and 11 years of age at the time of onset. The highest incidence of the disease in our series occurred during the first three years of life. This might suggest the possibility that the biologic quality of young renal tissue is a predisposing factor.

Sixty-one per cent of the children were males. Twenty boys as compared to fourteen girls, does not, however, permit a conclusion as to sex predilection.

In 70 per cent of the children the first symptoms of nephrosis were observed during the first six months of the year, one-half of these having started in March and April. The prevalence of infections during these months might indicate a seasonal relationship but more data would be necessary to make this a fact.

Thirty-one of the children were white and 3 (9 per cent) were Negroes. Considering that among 434 consecutive admissions during 1944, 48 per cent of the ward population consisted of Negro children, it seems justifiable to conclude that lipemic nephrosis is rarely seen in the Negro race.

The *chronicity of the disease* is usually so outstanding that many clinicians speak of "chronic" nephrosis, which is unfortunately true in the majority of cases. Ten of our patients were observed throughout the course of the disease which varied from nine months to three and one-half years. But we have seen three patients who suffered from lipemic nephrosis for only two, four, and twelve weeks, respectively. Therefore, chronicity is not always characteristic and should not be included in naming the illness. Two of the children who had such a short course recovered spontaneously. Chart 1 shows the correlation of the blood chemistry and albuminuria in one of these patients during the process of rapid healing. An albuminuria of 17.6 Gm. protein per twenty-four-hour urine decreased overnight to 0.44 Gm. and the next day to 0.07 Gm. Three days later the urine was entirely free of albumin. In this case we are not even able to suspect the cause of the unexpected overnight cure. The third child, 1 year of age, received 3 grains of thyroid extract daily and after three to 7 days had fever, a marked loss in weight, acidosis and diarrhea. The administration of thyroid extract was discontinued, intravenous fluids administered, and food withheld. After this child had recovered from the intoxication, the urine was free of albumin and two weeks later the blood chemistry had returned to normal. She has remained well.

It has been claimed that unexpected cures may occur quite frequently under the influence of severe infections. It has even been recommended² to delay chemotherapy for that reason. We have cared for children ill with nephrosis complicated by severe infections such as pneumococcic peritonitis, pneumonia, empyema, otitis media, and others, but we have never seen a sudden cure follow such infections. Consequently we cannot support such a recommendation. Mumps occurred in two of our children and pertussis in two others. During the presence of these infections the edema increased markedly and the blood chemistry became worse. After they recovered from these infections their

nephrotic status was not worse, but certainly not better than it had been previously. Improvements and even cures in lipemic nephrosis have been reported⁵ when the disease was complicated by measles. We have seen four nephrotic children contract measles in spite of one or two injections of 4 c.c. of immune globulin. One child died of a toxic pneumonia following measles. One other who became worse in every respect while he had morbilli recovered, but the status of the nephrosis had been unaffected. The observations made in the two remaining patients were quite astonishing. One patient (Chart 2), who had had a marked albuminuria uninterruptedly for over one year, contracted measles, and during this illness the urine was free of albumin for four days.

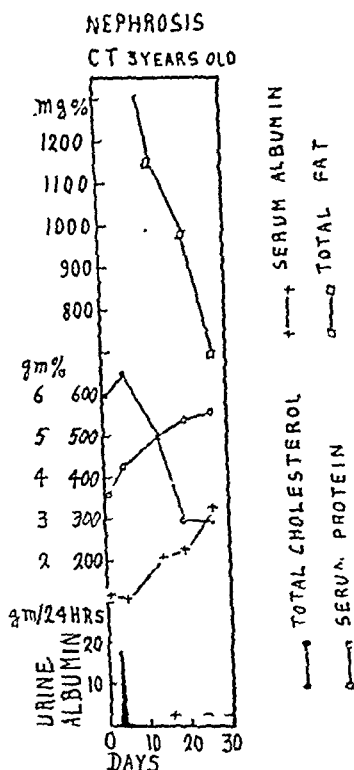


Chart 1.—Spontaneous overnight cure of lipemic nephrosis. Urine became free of albumin within three days, blood chemistry became normal within the next four weeks.

The total lipids and cholesterol decreased considerably, the serum proteins increased within three weeks to 4.5 Gm., and ascites and edema diminished rapidly. However, bronchopneumonia reversed the improvement to the premeasles status. This episode did not have any further influence on the course of her disease. The second patient, 2½ years old (Chart 3), improved even more remarkably. This boy's urine was free of albumin for eighteen days and the improvement in the blood chemistry was even more evident. A mild pharyngitis developed; however, he had a relapse and has had 1 plus to 2 plus albuminuria ever since. The rapidity with which the urine became albumin-free in these two children

was most spectacular. The unknown mechanism which causes the massive albuminuria of nephrosis must, therefore, be quite labile. If a severe infection, or measles, or thyroid intoxication can occasionally cause a sudden cure in nephrosis, it is well to consider that this may also happen spontaneously.

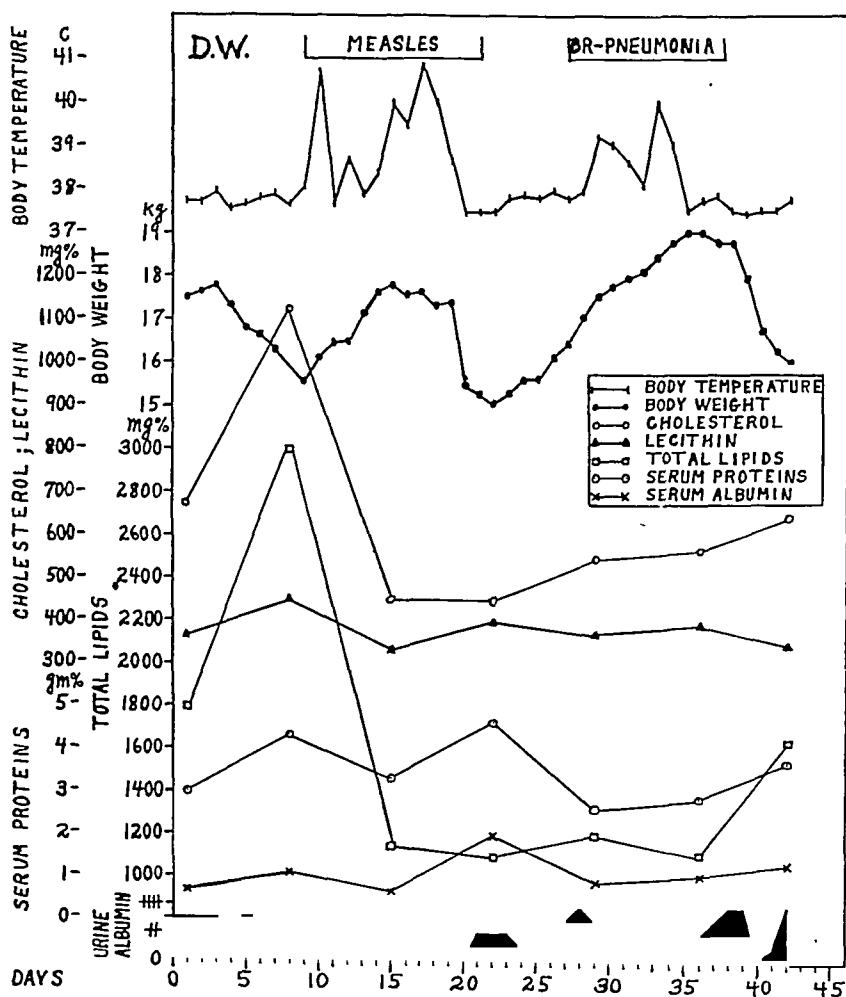


Chart 2.—Temporary improvement of lipemic nephrosis under the influence of measles.

The development of *edema* is, in nephrosis, generally explained by the diminished oncotic pressure resulting from the hypoproteinemia. In 1932, however, Fremont-Smith⁶ pointed out that this mechanism is only one factor which facilitates edema formation "when the kidneys fail to respond to fluid intake with a normal diuresis." We can substantiate this conclusion with numerous observations. Four cases (three cases, Chart 4, and one, Chart 2), clearly demonstrate how the weight of these children varied independently from the hypoproteinemia and hypoalbuminemia. In accordance with another observation made

by Fremont-Smith and associates⁶ we frequently found that if our patients acquired an infection, edema developed in from one to three days before the fever, at a time when serum protein and albumin values remained unchanged. We, furthermore, saw the edema disappear under the influence of daily plasma infusions (Chart 4) before the serum protein values had even begun to rise. The hypoproteinemia and hypoalbuminemia, therefore, cannot entirely explain the development of edema in nephrosis.

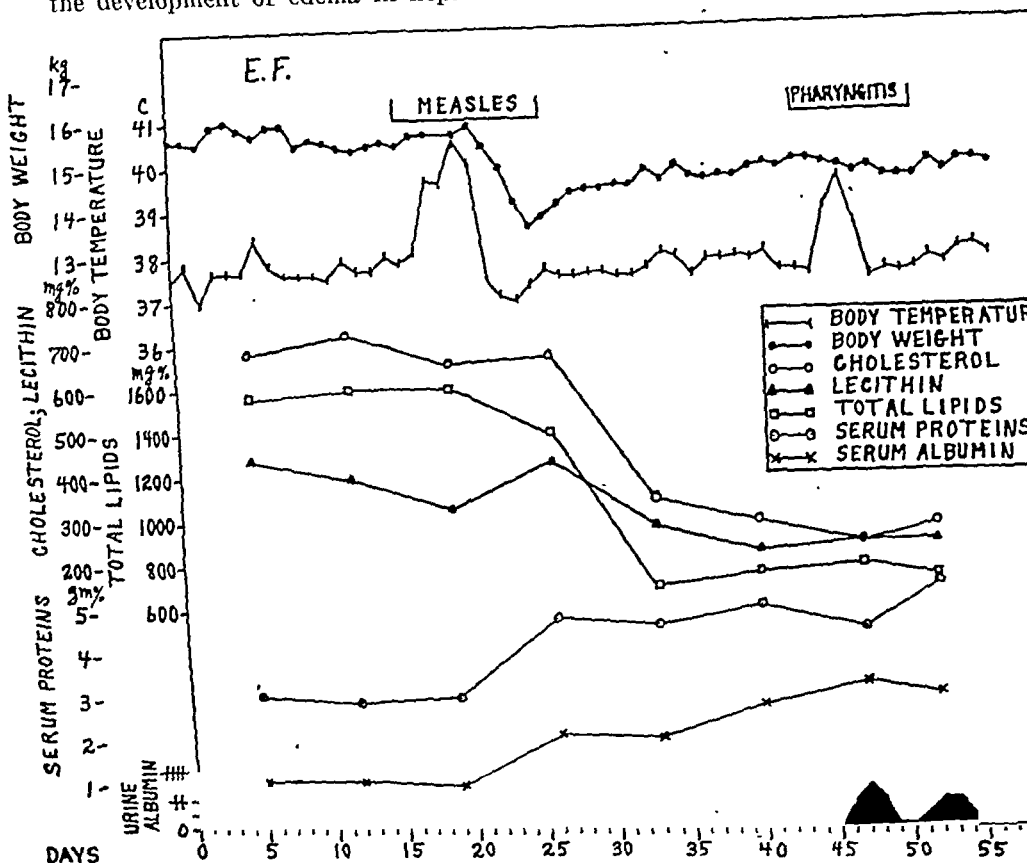


Chart 3.—Temporary improvement of lipemic nephrosis under the influence of measles.

The chemical composition of *ascitic fluids* obtained from three patients were analyzed. Fluid and serum were obtained on the same day for chemical analysis. The corresponding values (Table II) made it quite clear that the fluid represented an ultra filtrate of the blood. The milky appearance of the fluid was due to only very small amounts of lipids which, as far as cholesterol and lecithin are concerned, were often below the range of exact determination.

The hypoproteinemia also has been held responsible for the development of the *hyperlipemia*. This hypothesis was based on Fishberg's⁷ experimental work. It has, however, been pointed out by others⁸ that this hypothesis cannot be sufficiently supported by clinical data. We agree with this objection and

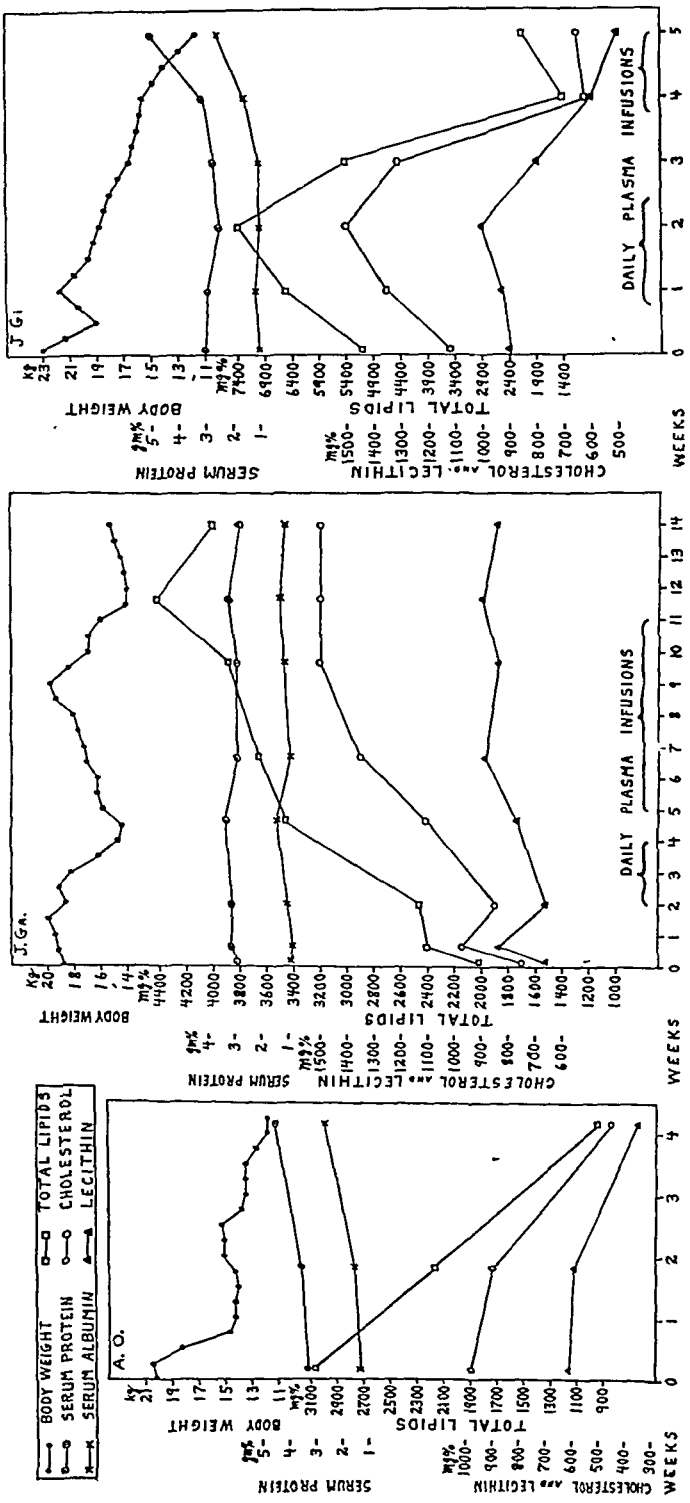


Chart 4.—Independence of body weight (ascites and edema) from hypoprotehemia and hypoalbuminemia.

TABLE II. COMPARATIVE CHEMISTRY OF ASCITES AND BLOOD SERUM IN LIPEMIC NEPHROSIS

NAME	ASCITES								BLOOD SERUM					
	PRO- TEIN	CHOL.	CHOL. ESTERS	TOTAL LIPID	LECITHIN	SPE- CIFIC GRAV- ITY	Na	Cl	SER. PROT.	CHOL.	CHOL. ESTERS	TOTAL LIPID	LECITHIN	
	GM. %	MG. %	MG. %	MG. %	MG. %		MG. %	MG. %	GM. %	MG. %	MG. %	MG. %	MG. %	MG. %
D. W.	0.05	10	0	85	6.0				3.0	554		1,810	320	
	0.075	30	13	110	9	1008	313		2.9	675	338	1,470	475	
A. S.	0.056	15	6	180	0		325	435	2.5	675	412	3,570	580	
	0.052	15	2	40	15	1008	300	440	2.6	810	412	4,900	700	
B. B.	0.065	23	8	40	20	1006	308	400	2.9	780	300	1,910	490	
	0.18	13		95	8		323	400	2.9	782		2,400	695	

refer to Chart 5. There is an example where between the two hundred and eightieth and three hundred and tenth days of illness, the cholesterol values increased concurrently with the serum protein values. There is no doubt that there is often an inverse development of lipid and serum protein values, but just as frequently we have noted a concurrent increase or decrease which is not in accord with Fishberg's⁷ theory. In 1928 Löwenthal⁹ expressed the opinion that lipemic nephrosis is a primary disease of the fat metabolism followed secondarily by nephrotic changes in the kidney. We accidentally observed a sudden relapse in a latent nephrotic patient as well as a sudden cure in another. Were Löwenthal's hypothesis correct, the hyperlipemia should have developed prior to the sudden increase of the albuminuria in the first child, while the hyperlipemia should have decreased before the albuminuria subsided in the second patient. As one can see in Charts 1 and 5 this was not the case. In Chart 5 it is shown that the hyperlipemia developed simultaneously with the sudden increase of the albuminuria, whereas the total lipid and cholesterol values started to decrease (Chart 1) with, or even shortly after, the disappearance of the albuminuria in this patient. Thus, Löwenthal's theory cannot be confirmed by our clinical observations.

How then is the nephrotic hyperlipemia to be explained? That it is endogenous in origin is certain.¹⁶⁻¹⁹ We gave a lipid free diet²⁰ to four children for a period of from two to four weeks, followed by a ketogenic diet for two weeks, varying the latter in ratios up to 3.5:1 in two patients without any influence on the blood lipid concentrations. Recent reports²¹ show that lecithin reduces the lipemia in xanthomatosis. On this basis, for an interval of three weeks, we gave from 30 to 40 Gm. of soya bean lecithin to three of our nephrotic children per os without observing any influence upon the blood lipid concentrations.

In 1942 Heymann¹⁰ advanced the hypothesis that the disease of the kidney itself might be responsible for the increase of the blood lipids found in nephrosis. This was based mainly on two experimental observations made in dogs. We found that (a) unilateral and bilateral nephrectomy, and (b) the parenteral administration of HgCl₂, potassium dichromate, and uranium nitrate gave rise to a hyperlipemia. This experimentally produced hyperlipemia like that found in nephrosis, involves total lipids, free and esterified cholesterol and phospholipids as well and is independent of changes in serum protein concentration.

It is not restricted to dogs; it has also been found in cats,¹¹ rats,¹² and monkeys.¹³ Because the same results may be obtained after extensive tissue necrosis, or occasionally after sham operations, or splenectomies,¹⁴ the kidneys are only one of several factors involved in a mechanism which regulates blood lipid concentration. If in lipemic nephrosis, however, none of the other factors are present which may give rise to an increase of the blood lipids, there is every reason to

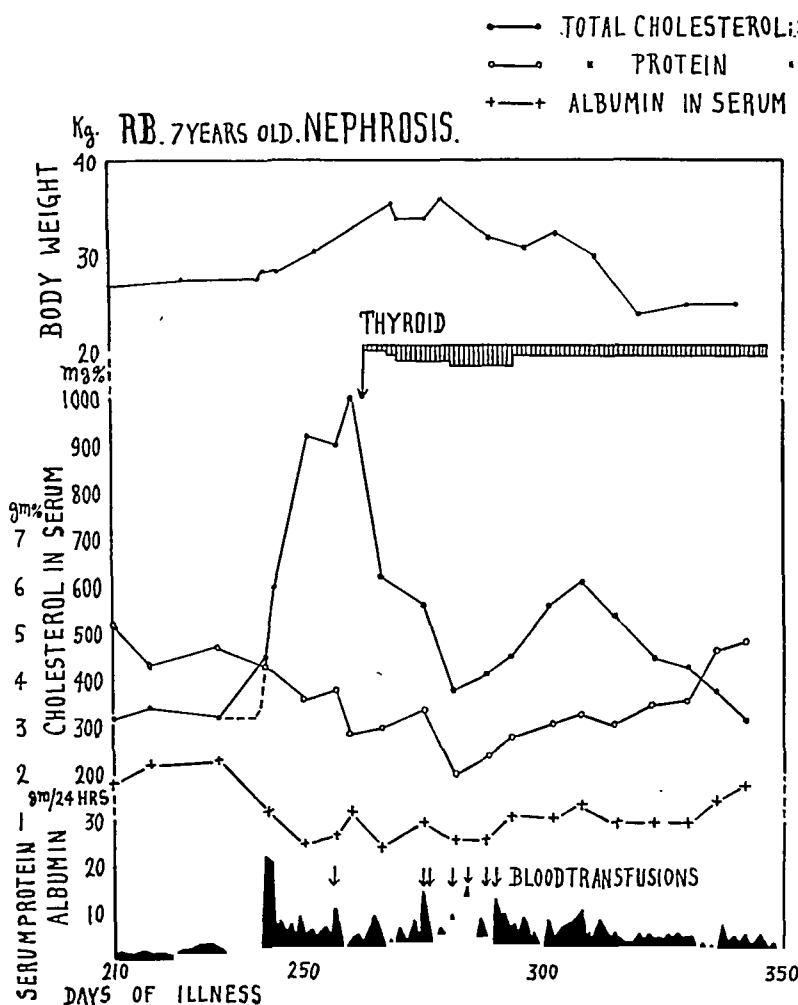


Chart 5.—Simultaneous development of hyperlipemia and albuminuria and influence of thyroid administration upon hyperlipemia and body weight (ascites and edema).

believe that the lipemia is of renal origin. This hypothesis is in agreement with the simultaneous development of albuminuria and hyperlipemia (Charts 1 and 5) and with the independent occurrence of hyperlipemia from hypoproteinemia (Charts 4 and 5). It is furthermore supported by the observation that in experimentally produced "nephrotic nephritis" in rats¹⁵ marked hyperlipemia was found.

Although the *therapy* in lipemic nephrosis is far from being ideal, one should not have a pessimistic and passive attitude. We advocate the following regime which controls the disease in most instances.

We have tried a great number of recommended procedures which proved to be of no practical value: Amigen, 20 Gm. daily, given orally to four children for three weeks, parenamine, 70 to 90 c.c., given intravenously daily for two to three weeks, calcium chloride or calcium gluconate orally or intravenously in large doses; vitamins A, B, C, and D, including liver extract and liver mush. Recently we have also discontinued the use of diuretics. The only ones which might be of some benefit are urea and mercurial compounds. They have such disadvantages that they do not compensate for the small advantage gained by a twenty-four- to forty-eight-hour lasting diuresis. Mercurial diuretics, if used at all in nephrosis, should be given intramuscularly²² only. We have seen two deaths following their intravenous use even in a 1:10 saline dilution. Because of the role which the pancreas might play in fat metabolism, two patients were given without benefit from 3 to 4 Gm. of pancreas extract* orally for three weeks. Finally on two different occasions we gave one child an intravenous infusion of 110 c.c. of reconvalescent plasma without success. This plasma had been obtained from a patient who had recovered from nephrosis for at least from three to four years. Because of the beneficial influence which febrile infections may occasionally have, we also have tried fever therapy in five instances for from ten to fourteen days without any success.

The administration of *thyroid extract* has had its place in the treatment of lipemic nephrosis ever since it was first recommended by Eppinger.²³ Its value has, however, not always remained unchallenged. We believe with many others²⁴ that in proper doses it will aid in eliminating the edema and in reducing the hyperlipemia. We have made it a rule to increase the dose by $\frac{1}{2}$ to 1 grain every 10 days until toxic symptoms are observed. We then decrease the amount by $\frac{1}{4}$ to $\frac{1}{2}$ grain and continue treatment with that subtoxic amount until the child is free of edema and the severity of the hypoproteinemia and the hyperlipemia has diminished for at least from two to three months. Hyperthermia, mild diarrhea, and tachycardia were the first toxic signs generally observed. During febrile infections thyroid medication is discontinued. We have treated ten patients according to this regime and have given as much as from 5 to 6 grains of thyroid extract to 3- to 4-year-old patients weighing from 15 to 20 kg. without observing any undesirable complications. It is understood that the progressive increase of the dose is not carried out to subtoxic amounts if the edema subsides before such symptoms have been produced. We are not in a position to say that thyroid medication alone will bring about the described result because we always gave it with some other form of treatment. We feel quite certain, however, that in eight of the ten patients so treated, loss in weight and decrease in the hyperlipemia were the results of thyroid medication. One example is shown in Chart 5.

Every nephrotic patient received a salt-poor diet with fluids limited to from 1,200 to 1,500 c.c. per twenty-four hours and containing 3 Gm. of protein

*Panteric tablets (Parke Davis & Company, Detroit, Mich.).

per kilograms body weight. We agree with Holt and Howland,²⁵ however, that the dietary treatment of nephrosis is of doubtful value.

If the edema and the ascites did not diminish within two weeks of bedrest, dietary treatment, and thyroid medication, we supported the outlined treatment with *daily intravenous infusions of from 2 to 250 c.c. of plasma* until the edema and the ascites were definitely decreasing. They were then given every second or third day until the edema had entirely disappeared. The plasma infusions combined with thyroid medication promptly eliminated the edema and the ascites in five and probably in two more of nine so-treated patients within two to six weeks. Consequently, we feel that the chance of actually relieving a nephrotic child of edema and ascites has been definitely improved. It takes a great amount of skill and endurance to find and to use the necessary veins* for daily infusions, but this treatment is without risk and of value in most instances. It has been pointed out previously that the reduction of edema and ascites may begin under the influence of plasma infusions before the plasma protein values begin to rise (Chart 4). Consequently the exact mechanism of this diuresis is not entirely clear.

Whenever the abdominal distention became too uncomfortable *abdominal paracentesis* was performed. The prophylactic administration of sulfonamides (0.1 Gm. per kilogram body weight) was started from one to two days previously. Using a 3- to 16-needle, from 1,500 to 3,000 c.c. of ascitic fluid have been removed within one to three hours. During the last three years this has been done over sixty times in eight different patients without any complication. The benefit is usually only temporary, the ascites reoccurring within from two to eight days. In one 2-year-old patient, however, we observed on two occasions that the withdrawal of abdominal fluid stimulated further recursion of the edema. In combination with sulfonamide prophylaxis we prefer this procedure to mercurial diuretics. The hazard is slight and the benefit greater if supported by daily intravenous infusions of plasma and thyroid administered in the proper dosage.

The greatest improvement in the therapy of lipemic nephrosis is the successful treatment of intercurrent infections with *sulfonamides or penicillin*. The presence of nephrosis does not represent a contraindication for the use of sulfonamides. With the great susceptibility of these patients to infections we used sulfathiazole and sulfadiazine within the last few years in practically every case without observing any unusual sensitivity to these drugs. If the dose was less than 0.2 Gm. per kilogram these sulfonamides were given without an alkali because of the desired restriction in salt intake. Once in one patient we observed an erythema nodosum-like rash associated with fever due to sulfathiazole. Later this same patient tolerated the same drug without any complications. We have used a full dose of 0.2 Gm. per kilogram body weight for short periods only and have continued treatment with 0.1 Gm. per kilogram often for several weeks, without renal complications. Lately we saw two patients who had pneumococcic peritonitis and who were successfully treated with penicillin and daily infusions of blood or plasma.

*The abdominal veins, often greatly distended, have been used frequently.

Within the last two years we have treated nine patients according to the described plan. We have achieved in all but one the elimination of edema and ascites with some improvement of their blood chemistry findings within two to six weeks. The symptomatic benefit is considerable, but the disease, of course, remains essentially uncured.

Internists are inclined to look upon a cured nephrotic patient as an extreme rarity. Pediatricians are more optimistic in that respect. Aldrich² speaks of a fifty-fifty chance and Kohn and Schwarz²⁶ found 25 per cent of their patients to have recovered completely, while Davison and Salinger²⁷ report a mortality rate of 30 per cent in their experience with twenty-six cases.

I believe that our results indicate that the *prognosis* of lipemic nephrosis is fairly good. Twelve patients were re-examined from one to seventeen years after their discharge from the hospital (Table III). Nine had been discharged more than three years before being re-examined. It can be seen that eight patients were found to be normal healthy individuals in whom no evidence of a persisting damage was found. In three additional patients our information rests upon written reports obtained from the mothers, which provided insufficient data indeed. From their reports it seems probable, however, that these three children have also been cured. Only one of these twelve patients had, twelve years after the onset, a severe renal disease with hypertension, fixed specific gravity, and renal retinopathy, the prognosis, therefore, being grave.

An interesting finding is that three out of eight children had after the original nephrotic disease orthostatic albuminuria five, six, and eight years later, respectively. Considering the rare occurrence of orthostatic albuminuria, we believe that this is more than an accidental observation. If orthostatic albuminuria is rather frequently observed in children who have recovered from nephrosis, it will be important to consider this fact when re-examining nephrotic patients. One patient (Schwarz and associates²⁶) who had been free of albuminuria for three years and whose urine again contained albumin later on might have been given a very different prognosis if it could have been shown that the albuminuria was of orthostatic origin and did not represent an actual nephrotic relapse.

Remembering the unexpected lability of the albuminuria observed in two nephrotic children who acquired measles and in whom the massive albuminuria subsided and subsequently reappeared overnight, remembering also the sudden cures of nephrosis reported by others and observed by us in three instances, and considering finally the observation of orthostatic albuminuria as the only residual nephrotic disease in three children, one wonders about the nature of the mechanism which permits large protein molecules to permeate into an otherwise protein free fluid and which at the same time seems to be quite easily reversible. On the basis of these observations we have tried the orthostatic or kyphotic position in three children ill with lipemic nephrosis to note whether it would have any effect on the albuminuria. It could not be shown, however, that kyphosis diminishes or that a pronounced lordosis increases protein excretion in the urine.

TABLE III. RESULTS OF RE-EXAMINATIONS AFTER ONE TO SEVENTEEN YEARS

DATA ON FIRST ADMISSION					DATA OBTAINED ON RE-EXAMINATION											REMARKS											
NAME	SEX	AGE IN YEARS	CLINICAL EVIDENCE OF ADDITIONAL NEPHRITIS	ALBUMINURIA AT TIME OF DISCHARGE	NO. OF YEARS AFTER DISCHARGE	AGE IN YEARS	URINE		BLOOD PRESSURE	ADDIS COUNT	SEDIMENTATION*	TOTAL LIPIDS	CHEMISTRY IN MG. PER 100 G.C. SERUM					EYEGROUNDS	ORTHOSTATIC ALBUMINURIA								
							ALB.	SED.					CHOLESTEROL	LECTHIN	N.P.N.		B.U.N.			CREATININE	UREA CLEARANCE	B.M.R.†					
J.M.	M	5	-	-	9	14	-	-	190/70	Normal	6	484	150	215	34	15.4	1.2	Normal	+18	Negative	-	Cured					
L.J.	F	2	-	+++	1½	3½	-	-	90/60		5	730	203	244	24		0.8			Negative	-	Cured					
C.T.	M	3	+	-	2	5	occ.+	-	100/60	Normal	11	500	160	150	30				+12	Negative	-	Cured					
D.F.	F	9	?	++	9½	19½	-	-	100/50	W.B.C.	27	516	147	135	30		1.1	Normal	+18	Negative	-	Cured					
S.H.	F	9	?	++	11	19	-	-	100/70	Normal		790	175	269	28		0.7			Negative	-	Cured					
F.K.	F	11	-	++	6½	18	-	-	100/70	Normal		480	100	394		7.5		Normal		Negative	-	Cured					
B.K.	F	1	-	-	5	6	-	-	112/60	Casts normal	Normal	455	150	215		12.4	1.3	Normal	-2	Negative	0.27† ++0.13†	Cured					
K.S.	M	2	+	++	8	10	-	-	100/70	Casts normal	5	560	199	316	30		1.0			Negative	++0.12†	Cured					
C.D.	M	5	?	+	1	6	-	-	120/90	Casts normal	6	700	270	250	32				-19	Negative	++	Cured					
R.B.	M	7	+	+	1	8	+	+	Out of town. Mother wrote that child is "doing splendidly."														Probably cured				
A.L.M.	F	6	-	++	17	23	-	-	110/50		10	Out of town.	Mother reported that child is doing well.														Probably cured
E.M.	F	9	+	++	12	21	++	W.B.C. ++	Out of town. Mother reported that patient is working hard, married, and has one healthy baby 2 years old.														Probably cured				
									190/40	W.B.C. Incr.	548	195	205		25	1.8	Greatly reduced	+27	Retinopathy		Chronic nephritis						

*Method of Westergren. First hour values.

†Grid standard per cent.

‡Gram per cent albumin in urine after twenty minutes orthostatic position.

Surveying our cases as to the prognosis of lipemic nephrosis we find ourselves in accord with Aldrich² who recommends that a rather optimistic attitude be taken toward the parents of these children. On the basis of our results we feel justified in prognosticating a better than fifty-fifty chance² for recovery.

Of the thirty-four patients we observed, ten (30 per cent) died from intercurrent infections in the acute phase of the nephrosis. Deducting these ten from the total number of children, and also the eleven who acquired the disease less than three years ago, there were twelve patients available for re-examination. Table III shows that only one of these children acquired a chronic nephritic renal disease in spite of the fact that from four to seven children showed signs of additional nephritis at some time during the course of the disease. It is, consequently, important to know that an episode of nephritis observed during the course of a primary lipemic nephrosis does not necessarily aggravate the ultimate prognosis. It is to be re-emphasized, however, that we have not included cases of primary nephritis which led to a secondary nephrotic syndrome. The ultimate prognosis in these instances might be much worse.

All in all we may conclude that the ultimate prognosis of genuine primary lipemic nephrosis is not so gloomy as is generally believed. The 30 per cent mortality rate which we have had in a series of cases observed during the last twelve years is not valid any more. Our series includes a majority of children who did not have the benefit of recent therapeutic achievements. These children were not treated with adequate doses of thyroid extract and daily infusions of plasma. The intercurrent infections which were the actual causes of death in ten of these patients would today have been successfully treated with sulfonamides or penicillin. The cause of death in lipemic nephrosis is either an intercurrent infection or terminal chronic nephritis. The latter is rare; occurring in our experience in approximately 8 per cent of the cases. The former accident previously was the fatal cause in the vast majority of the cases. Of eleven patients which we treated during the last three years with sulfonamides and penicillin only one died of toxic pneumonia following measles. We, therefore, could come close to the actual situation of today, by stating that the mortality rate has been reduced to between 15 and 20 per cent.

SUMMARY

1. Thirty-four children suffering from primary lipemic nephrosis have been observed within the last twelve years. At the onset, 64 per cent were under 3 years of age showing clearly the young child's predilection to the disease. Twenty-one per cent were from 4 to 7 years and 15 per cent from 9 to 11 years of age when the disease began. These figures demonstrate its decreasing incidence among older children and explain its rare occurrence in adults.

2. Lipemic nephrosis is rare in the Negro race.

3. Six post-mortem examinations are discussed. The microscopic examination in three showed no signs of inflammatory disease and azocarmine stains revealed normal, not thickened glomerular basement membranes. In the three remaining cases renal inflammatory disease was found in addition to definite nephrotic changes. The nephritis in these instances was classified as interstitial

and pyelonephritic in type. Only one of these showed slightly thickened basement membranes. Together with the clinical observations it is concluded that there is (1) a primary lipemic nephrosis, (2) a primary nephritis which develops secondarily the nephrotic syndrome, and (3) a primary lipemic nephrosis which develops secondarily nephritis. The inflammatory lesion in this latter instance is usually of the interstitial and pyelonephritic type.

4. The chronicity of the disease should not be included in the terminology. Three children are reported who were ill for only two, four, and twelve weeks. Two of these healed spontaneously whereas the third cure followed an overdose of thyroid extract.

5. In spite of severe intercurrent infections frequently observed in our cases we cannot state that they either improved or cured the nephrotic disease. Thus, it is not recommended to delay chemotherapy in intercurrent infections.

6. Mumps and pertussis occurred in four of our nephrotic children. A temporary aggravation was seen during the acute phase of these infections. One out of four children who acquired measles died from pneumonia, whereas two others became albumin-free for from four to eighteen days. They temporarily lost the edema and the ascites and there was a transient improvement in the blood chemistry. The fourth patient who had measles temporarily became worse. Even though it is admitted that measles may temporarily improve the condition of a lipemic nephrosis, the "rumor" that it cures nephrosis cannot be substantiated.

7. It has been shown that hypoproteinemia and hypoalbuminemia do not entirely explain the formation of edema in nephrosis. The hypoalbuminemia is only one of several factors involved in this mechanism.

8. The endogenous origin of the hyperlipemia of nephrosis is shown by the fact that it is not affected by diets of either low or high fat ratios, nor does the nephrotic hyperlipemia decrease when 30 to 40 Gm. of soya bean lecithin is given for four weeks.

9. Clinical data do not support the hypothesis that the hyperlipemia is due to the hypoproteinemia, nor do they agree with the conception that the nephrotic kidney damage is due to a primary disturbance of fat metabolism. It has been shown in animal experiments that the kidneys are involved in a mechanism which regulates blood lipid concentration. On the basis of these studies the hypothesis is advanced that the hyperlipemia in nephrosis is of renal origin.

10. As for therapy, we recommended a salt-free diet containing 3 Gm. of protein per kilogram body weight, and a fluid intake limited to 1,200 to 1,500 c.c. in combination with thyroid extract. This is increased every ten days by $\frac{1}{2}$ grain. As soon as toxic symptoms are observed, the dose is reduced by $\frac{1}{4}$ to $\frac{1}{2}$ grain and kept as a maintenance dose for two to three months. If after two weeks of bedrest, thyroid medication and dietary treatment, the edema and the ascites have not appreciably decreased, daily intravenous infusions of from 200 to 800 c.c. of plasma are given and continued for from three to six weeks if necessary. Under the prophylactic administration of 0.1 Gm. per kilogram body weight of sulfadiazine or sulfathiazole, abdominal paracentesis may be performed

without risk, if the abdominal distention is excessive. A 3- to 16-needle is recommended for this purpose and will avoid keloid scar formation so often observed after the use of trocars. Intercurrent infections are treated with 0.1 to 0.2 Gm. of sulfonamides per kilogram body weight or with penicillin if indicated.

11. Twelve children were re-examined up to seventeen years after their first discharge from the hospital. Only one of these had a severe chronic nephritis. Eight were positively and three probably cured. Three out of the eight completely re-examined patients had an orthostatic albuminuria five, six, and eight years, respectively, after the onset of the nephrosis.

12. The ultimate prognosis of primary lipemic nephrosis is better than is generally believed. The mortality rate of 30 per cent which we have had in our series of thirty-four patients is not valid today. Most of these patients were treated before the described therapeutic regime was instituted. According to our observations in eleven cases treated during the last three years the present mortality rate would be approximately between 15 and 20 per cent.

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THE INDUCTION OF VITAMIN C SUBNUTRITION

A COMPARISON OF INTRADERMAL TESTS WITH PLASMA ASCORBIC ACID LEVELS

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SCURVY is rare, but vitamin C subnutrition is sufficiently common to warrant serious attention not only by students of nutrition but also by practicing physicians. In vitamin C subnutrition there are no clinical signs or symptoms of scurvy. The diagnosis can be made only by the history and laboratory findings. In the history one looks for the four frequent factors in the production of vitamin C subnutrition:

1. An inadequate dietary intake of vitamin C.
2. A faulty absorption as in diarrhea and persistent vomiting.
3. An increased demand because of an increased metabolism as in hyperthyroidism and prolonged febrile diseases.
4. An increased urinary excretion which washed out the ascorbic acid as in large intravenous infusions before and after operations.

The plasma ascorbic acid level is the most frequently used laboratory determination for vitamin C subnutrition. Interpretations of the levels differ with the various authorities. A level of less than 0.2 mg. per cent is thought by most to be well below the average. Levels of more than 0.3 mg. are difficult to interpret since they vary with so many factors.

We have reported¹ recently on an intradermal test which would qualitatively indicate vitamin C subnutrition states. The test is based on the intradermal injection of a dye which will be decolorized by vitamin C. Slow decolorization of the dye would indicate that the tissues have an insufficient amount of vitamin C. Rapid decolorization would indicate a sufficient amount. In our test enough of a N/300 solution of sodium 2,6-dichlorophenol indophenol is injected to raise an approximately 4 mm. wheal (Fig. 1). A skin test time (the length of time required for the dye to disappear) of fourteen minutes or more suggests a definite degree of tissue unsaturation, from ten to thirteen minutes is borderline, and less than nine minutes indicates a normal amount of vitamin C in the body tissues (Fig. 2).

Different laboratory tests give information on various aspects of the vitamin C nutritional state and will not always correlate. There has been a tendency to overestimate somewhat the value of the blood level of vitamin C in appraising nutritional status. It is an important aid but does not tell the entire story. Kruse² states "it should be clear that there is no necessarily high correlation between data derived by different methods on the same deficiency disease. They

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provide information on different aspects and states of the disorder. Unfortunately, this fact has not been appreciated. Rather, it has been thought that various methods applied to the same deficiency disease should yield similar data. On this basis it has become the practice to test the validity of a method by comparing its results with blood values. This procedure is entirely unsound. When it is remembered that blood values shift rapidly and may fluctuate intermittently, while tissue changes vary slowly, there should be no expectation of



Fig. 1—Technique of the intradermal test.

identical results. . . . Values on the concentration of a vitamin in the blood reflect very sensitively the recent dietary habit as well as other conditioning factors. They may change not only with season but also within shorter periods; they may fluctuate. . . . Potent therapy will produce maximum blood levels and entirely restore bodily saturation in several weeks, but will completely repair the slightest chronic tissue lesion only in months."

In 1940, human scurvy was induced by Lund and Crandon³ in a gallant and classic experiment. On a vitamin C free diet, they found that the plasma

ascorbic acid level fell to zero in forty-two days. The ascorbic acid disappeared from the white blood cells in 122 days. In about five months, petechial hemorrhages appeared around the hair follicles of the legs. In the sixth month marked fatigability developed. Pijoan and Lozner⁴ found similar results in six subjects placed on a diet lacking in vitamin C but normal in all other respects. Johnson and associates⁵ had a group on a vitamin C deficient diet in whom the serum ascorbic acid was zero in all but one subject by the end of the fifth week, and in this case it became zero by the end of the seventh week. In 1939, Rietschel and Mensching⁶ reported that one of them lived for 100 days on a vitamin C free diet. Before starting the diet, his blood level was 0.72 mg. per cent and at the end of 100 days was practically zero. During the entire experiment he felt as well as ever and recovered from a slight cold without any difficulty. They further asserted that the "danger zone only" begins after the blood level has reached the zero point. They point out that Widenbauer observed two infants who only developed scorbutic symptoms eight weeks after the blood level had been at the zero point.

PLAN OF STUDY

In our studies, we did not use an absolutely vitamin C free diet. We removed only citrus fruits and tomatoes from the diet. This approximated the ordinary living conditions of many of the children who have been seen in our clinics.

Sixteen children were kept under close observation in institutions. Their life approximated home environment as closely as possible. They attended school, played, exercised, and rested. The diet was adequate in all the essential elements of nutrition except vitamin C. The average daily diet was found to contain 2,150 calories of which 85 Gm. were protein, 237 Gm., carbohydrate, and 96 Gm., fat. The vitamin and mineral contents were equal to or above those recommended. It was very difficult to compute accurately the vitamin C content in this diet which contained no citrus fruits or tomatoes because of the effects of such things as cooking, standing, and mincing on the vitamin C content. There was probably at no time more than from 10 to 15 mg. of ascorbic acid in the diet per day.

Before being placed on the vitamin C deficient diet, the children were given from 50 to 300 mg. of ascorbic acid a day until the skin test time and blood were within normal limits. After the vitamin C deficient diet was started, plasma ascorbic acid determinations and intradermal tests were done at weekly intervals. When the plasma ascorbic acid went to approximately 0.2 mg. and the skin test was longer than fourteen minutes, ascorbic acid in various dosages were administered until the skin test and plasma ascorbic acid returned to normal.

RESULTS

Sixteen children ranging in ages from 5 to 11 years of age were given from 50 to 300 mg. of ascorbic acid daily until the skin test and plasma ascorbic acid levels were within normal range. This was usually accomplished in from one to three weeks. Then the diet which contained no citrus fruits or tomatoes

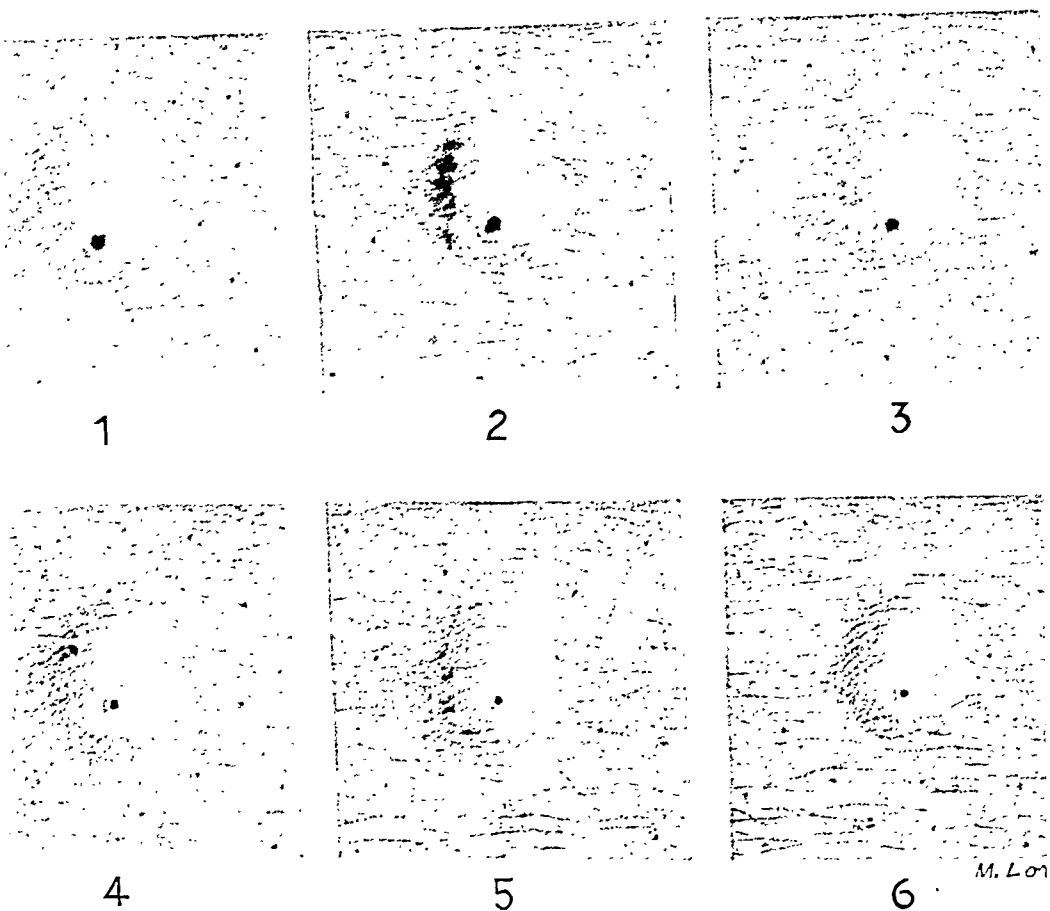


Fig. 2.—Intradermal test in patient with vitamin C subnutrition (painted from life).

1, Immediately after injection; 2, 4 minutes after injection; 3, 8 minutes after injection; 4, 12 minutes after injection; 5, 16 minutes after injection; and 6, 17½ minutes after injection, disappearance of all blue color except the pin-point darker blue spot where the needle entered the skin. The pin-point darker blue spot is not to be considered in determining the decolorization time.

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was begun. The results of the skin and blood tests before the diet, during the diet, and after administration of various amounts of ascorbic acid are given in Table I. Before beginning the diet, the skin test times were nine minutes or less in fourteen children and eleven minutes in two children. The blood ranged from approximately 0.5 mg. to 1.9 mg. During the diet, the skin test times became prolonged beyond fourteen minutes in all children. The skin test times were again shortened to normal following the administration of from 25 mg. to 200 mg. of ascorbic acid per day. During the diet most of the plasma levels of ascorbic acid fell. In Case 1, it took eight weeks for the level to reach zero. In Case 8, it required only two weeks to reach 0.11. In Case 14, the blood level was .98 mg. at the end of six weeks on the diet. In Cases 15 and 16, no blood tests were done. The blood levels rose following the administration of ascorbic acid.

The children felt well during the entire study and there were no abnormal physical findings. The blood counts and x-rays were essentially normal. In five cases the serum phosphatase was found to be within normal limits. Gross and some biomicroscopic examinations of the gums revealed some of the gingival manifestations of vitamin C deficiency described by Kruse,⁷ however, no attempt was made at this time to evaluate and correlate these findings.

COMMENT

The entire significance of vitamin subnutrition is unknown at present. We cannot hold with those who believe that vitamin deficiencies should be treated only when they present actual clinical findings. It seems likely that vitamin subnutrition persisting over some time will produce biochemical changes that would mitigate against good tissue function. Also it is clear that clinical deficiency can easily follow vitamin subnutrition.

In our studies, we did not use an absolutely vitamin C free diet. It is important to note that subnutrition can be induced on a diet which lacks citrus fruits and tomatoes. It took eight weeks for the plasma ascorbic acid to fall to zero. This is two more weeks than it took in comparable studies on a diet completely free of vitamin C. We can postulate that it would take a much longer time for clinical signs and symptoms of vitamin C deficiency to appear with a mildly deficient diet than with a markedly deficient diet.

Individuals have different vitamin C requirements. On the same diet and under similar basal conditions, they will become deficient at different times. Vitamin C requirements are dependent not only on age, height, and weight, but also on a complex of factors—endocrine, nervous and others—which govern an individual's vitamin C metabolism. These factors we are attempting to evaluate in other studies. It is necessary, therefore, to individualize estimates for the vitamin C intake in prophylaxis and treatment of vitamin C deficiencies.

In our studies, both the plasma levels and the skin tests have followed the induction of vitamin C deficiency and the reversal with administration of ascorbic acid. It is argued that our skin test is only a qualitative test while the plasma level is more quantitative. From a practical standpoint, we have received just as much information from the skin test. Since the skin test is

TABLE I

NO. SEX	AGE (YR.) RACE	DAY DIET STARTED	WEEKS AFTER DIET STARTED												Skin min. Blood mg. A. A.* mg. therapy	
			1	2	3	4	5	6	7	8	9	10	11	12		
1	m	7	7.5 1.47	9.3 .81	8.9 .46	9.1 .51	8.1 .53	12.0 .45	15.5 .30	16.5 .20	16.8 .00	15.2 .12	15.7 .34	9.8 .54	9.4 .55	Skin min. Blood mg. A. A.* mg. therapy
2	f	8	5.2 .54	16.3 .55	15.4 .70	10.6 .30	12.3 .40	17.4 .42	17.8 .12	17.1 .23	9.6 .43	9.2 .44	8.3 .73	5.9 .74	5.0	Skin min. Blood mg. A. A.* mg. therapy
3	f	10	9.4 .50	15.9 .31	18.8 .36	15.3 .18	10.1 .65	10.2 .85	7.6 1.49	8.5 1.12	5.4 1.41	5.4 1.00	5.4 1.00	5.4 1.00	5.4 1.00	Skin min. Blood mg. A. A.* mg. therapy
4	f	8	11.2 .94	21.8 .36	17.1 .20	18.6 .21	19.4 .43	12.8 .33	10.1 .75	7.9 .98	7.9 .98	7.9 .98	7.9 .98	7.9 .98	7.9 .98	Skin min. Blood mg. A. A.* mg. therapy
5	m	6	8.3 .46	8.3 .38	15.8 .19	16.7 .20	15.5 .21	12.9 .36	14.6 .18	8.5 .52	8.5 .52	8.5 .52	8.5 .52	8.5 .52	8.5 .52	Skin min. Blood mg. A. A.* mg. therapy
6	f	8	11.0 .48	17.0 .52	19.0 .22	16.0 .23	15.2 .27	13.8 .20	16.7 .20	16.7 .20	16.7 .20	16.7 .20	16.7 .20	16.7 .20	16.7 .20	Skin min. Blood mg. A. A.* mg. therapy
7	m	8	7.0 .95	16.9 .32	16.4 .34	18.0 .11	7.7 1.47	7.7 1.47	7.7 1.47	7.7 1.47	7.7 1.47	7.7 1.47	7.7 1.47	7.7 1.47	7.7 1.47	Skin min. Blood mg. A. A.* mg. therapy
8	m	10	7.7 1.30	11.7 .32	14.1 .11	22.3 .11	17.3 .33	9.8 1.27	9.8 1.27	9.8 1.27	9.8 1.27	9.8 1.27	9.8 1.27	9.8 1.27	9.8 1.27	Skin min. Blood mg. A. A.* mg. therapy
9	f	6	7.0 1.84	9.1 1.02	12.2 .63	24.2 ----	21.9 .36	19.1 .23	10.7 .40	8.5 2.29	7.8 .97	7.8 .97	7.8 .97	7.8 .97	7.8 .97	Skin min. Blood mg. A. A.* mg. therapy
10	f	7	7.2 1.15	14.5 1.14	14.8 .75	15.6 .24	12.7 .60	7.2 ----	5.8 .97	5.8 .97	5.8 .97	5.8 .97	5.8 .97	5.8 .97	5.8 .97	Skin min. Blood mg. A. A.* mg. therapy
11	m	11	6.8 1.95	9.5 .62	14.1 .31	17.0 .22	17.9 .29	8.6 1.07	7.8 1.89	7.8 1.89	7.8 1.89	7.8 1.89	7.8 1.89	7.8 1.89	7.8 1.89	Skin min. Blood mg. A. A.* mg. therapy
12	f	8	6.4 1.77	7.7 .88	8.1 .57	7.4 .57	17.4 .49	14.4 .37	14.4 .37	12.2 9.9	6.6 1.63	6.6 1.63	6.6 1.63	6.6 1.63	6.6 1.63	Skin min. Blood mg. A. A.* mg. therapy
13	f	10	6.6 .99	12.8 .51	16.5 .98	16.9 .88	14.4 .39	10.8 1.71	6.1 1.84	6.1 1.84	6.1 1.84	6.1 1.84	6.1 1.84	6.1 1.84	6.1 1.84	Skin min. Blood mg. A. A.* mg. therapy
14	m	5	6.8 1.00	10.7 1.26	10.8 1.08	12.4 ----	15.0 .85	14.3 .76	14.8 .98	5.7 1.30	5.7 1.30	5.7 1.30	5.7 1.30	5.7 1.30	5.7 1.30	Skin min. Blood mg. A. A.* mg. therapy
15	m	6	9.5	16.5	15.0	14.8	15.2	9.5	9.0	11.7	4.0	3.8	3.8	3.8	3.8	Skin min. Blood mg. A. A.* mg. therapy
16	m	8	6.3	7.2	8.8	17.2	15.1	16.8	25	50	50	50	50	50	50	Skin min. Blood mg. A. A.* mg. therapy
17	m	8	6.3	7.2	8.8	17.2	15.1	16.8	25	50	50	50	50	50	50	Skin min. Blood mg. A. A.* mg. therapy

*Ascorbic acid.

cheap, easy to perform and quickly read, it can be used frequently in following a case in practice. We have not done vitamin C concentrations in the white cell layer because that only falls late in the course of vitamin C deficiency.

SUMMARY AND CONCLUSIONS

1. Vitamin C subnutrition was induced in sixteen children by a diet which lacked citrus fruits and tomatoes.

2. The plasma ascorbic acid levels and intradermal test followed reliably the induction of vitamin C deficiency and returned to normal with administration of ascorbic acid.

3. The intradermal test is cheap, easy to perform, and quickly read.

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A VISION TEST FOR PEDIATRICIAN'S USE

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THE evaluation of vision is a desirable part of the periodic examination of children: the pediatrician should be prepared to screen out those of his patients who require the services of an eye specialist. At present this part of the pediatrician's examination is often omitted by him: his tendency has been to avoid it because it is considered to be a field requiring special equipment and training and because it is generally regarded as requiring too much of his time. However, in the work which we have done with vision testing programs it has been found that a fairly complete test can be given within a four-minute interval^{1, 2, 3} and recently certain pediatricians have asked whether this test would be suitable for their use. It seems to us that pediatricians would find it practical for use in their offices, but to simplify this test further one part has been omitted and yet its efficiency only slightly impaired.

Many children at age 4, and almost all by age 5, can be tested in this manner; in the case of those who do not know their letters the illiterate symbol E chart (in which the child indicates the direction of the letters) should be used. The test is equally applicable to older children. The usual medical examination includes an inspection of the external eye, the eye movements, the pupils, and a search for the presence of inflammation or other gross pathology as well as the use of the ophthalmoscope. In this particular sphere we have no suggestions to make, but in regard to those subtle conditions which are capable of producing eye dysfunction and which are not uncovered by the usual eye inspection, the method of testing described herein will be found effective.

In general there are three conditions in the eye of normal appearance which can cause difficulty: (1) lowered *visual acuity*; (2) the presence of a *latent refractive error* (hypermetropia, "farsightedness") in which normal vision is maintained by an excessive compensatory effort capable of producing "eye strain"; (3) those *latent muscle imbalances* which are obscured by a strong compensatory effort to avoid diplopia and which also can be productive of "eye strain." In a group of 137 adolescent boys referred to an eye specialist,⁴ 74 per cent fell into the first category, 20 per cent into the second, and 6 per cent into the third. An examination of 797 boys,³ 35 per cent of whom already had glasses, showed that 22 per cent failed the visual acuity test without glasses, an additional 5 per cent failed the test for a latent refractive error (hypermetropia); and an additional 4 per cent failed the muscle imbalance test. The percentage of individuals falling into any of these categories depends in part on the number which have previously had a thorough eye examination: the

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figures given were for privileged preparatory-school boys, many of whom had previously had adequate attention. The inclusion of a test of latent hypermetropia is important: in a recent survey³ it was found that about 7 per cent of the 518 boys who did not have glasses passed the visual acuity test but failed the latent hypermetropia test. Thus, while these individuals had 20/20 vision, there still remained a condition capable of producing symptoms. It should also be emphasized that the possibility that eye strain is present cannot be eliminated just because the patient is wearing glasses: eye strain cannot be excluded as the source of symptoms unless one is sure that all of the existing refractive errors have been corrected adequately.

I. *Lowered visual acuity* may be caused by (a) any degree of "near sightedness" (myopia), (b) high amounts of "far sightedness" (hypermetropia), and (c) moderate to high amounts of astigmatism. Myopia may cause a significant reduction in visual acuity but it rarely produces headache or "eye strain." On the other hand, high amounts of hypermetropia or moderate to high amounts of astigmatism will not only decrease the visual acuity but will also frequently give rise to such symptoms as headache, inability to concentrate, nausea, vertigo (not exaggerated by change in posture) and many vague as well as definite complaints of ocular asthenia generally referred to as "eye strain." Part one of the test to be described serves to screen out individuals having reduced visual acuity.

II. A significant refractive error (*hypermetropia*, "far sightedness") may be present and yet the patient can still have normal visual acuity. In such cases excessive exertion of one's accommodation corrects the refractive error. Hypermetropia is corrected by convex lenses. Since accommodation of the crystalline lens is in effect a source of supply of convex power (the curvature of the lens becoming more convex through the action of the ciliary muscle) the child learns early and subconsciously to correct his own hypermetropia so that he can have clear sight. However, the sustained excessive use of his accommodation may cause fatigue and other symptoms which the child will tolerate in order to maintain good vision. These resultant symptoms may be the same ones mentioned in the preceding paragraph. Very often the excessive use of accommodation may in turn upset the relationship which it normally has with the convergence action of the eyes. For this reason an ocular muscle imbalance (accommodative esophoria) may be introduced and it may further increase the effort necessary to maintain normal vision. As a result of this train of events the symptoms may become out of proportion to the underlying cause and their basis not be suspected because the sight is well within normal limits. Part two of the test is designed to screen out patients who have this condition. Its *modus operandi* is simple. Convex lenses of a predetermined power are placed before the eyes. If the patient has hypermetropia (which is correctible in part or whole by the convex lenses) he will "accept" them, i.e., he will be able to read the test letters through them. This is because his accommodation will relax its overexertion and will allow the lenses to supply the needed convex power. If, on the other hand, his error is less than the power of the test lenses, or if he has no hyperopic refractive error, he will be unable to read the test letters. A homely comparison may be drawn with

the type of paper napkin holder found in some restaurants. In these a concealed spring gives the impression of an adequately full holder whether there be only one or many napkins present. Similarly hypermetropia, because of its concealed spring (accommodation), yields normal visual acuity and gives the impression that the eyes are normal. In the case of the napkin holder a simple instrument to determine the need for more napkins ("help") would be a suitably sized block of wood. When this could be inserted in the napkin compartment (i.e. "accepted") it would indicate the need for more napkins ("help"). In a like manner the pair of convex lenses are used to test the need for "help" in the eye. If they are accepted (i.e., if the eye is able to read test letters through them) the eye needs help. Ability to read test letters through the lenses is, therefore, an indication for referral to an eye specialist, whereas failure to read the test letters through them represents a normal performance.

III. *Latent muscle imbalances* can also cause symptoms of ocular discomfort. The direction of the two eyes must be precisely coordinated if one is to have single vision, i.e., to make the two eyes act as one. The "fusion sense" is the name of that driving force which keeps the eyes in proper alignment. The ease of coordination of the two eyes may vary in different individuals by virtue of many factors including shape of the head, distance between the eyes, and others. Thus the "fusion sense" may have to work excessively under certain conditions in order to maintain single vision. This draining from the reservoir of fusion power may cause ocular symptoms varying in degree from eyes which tire easily to discomfort of considerable magnitude. Simple methods for detecting latent muscle imbalances have been described elsewhere.^{1, 3}

The Massachusetts Vision Test¹ and its modification³ were devised for the detection of all three of those defects. However, in order to offer an eye test which would be more practical for a pediatrician's office use, we have decided to omit that part having to do with muscle imbalance. This permits the elimination of the special light source, the use of certain special lenses, and of testing conditions such as darkening of the room. We appreciate that this represents a compromise, but we feel that only a small percentage of the total which would be referred to an eye specialist will be lost, and that this is much more desirable than suggesting a test whose extra equipment and conditions, although relatively simple, might restrict its use in everyday practice.

METHOD OF TESTING

The test is divided into two parts. Failure in the first part is sufficient for referral to an eye specialist and consequently removes the necessity for carrying out the subsequent procedures. This test can be effectively administered by an office assistant after only a short period of instruction. The entire test can be completed within a very few minutes.

Part I. Visual Acuity.—A clean letter chart* is hung whenever possible

*The following are among the charts which have been approved by the A. M. A.: American Optical Company—Distance Test Chart No. 1930 and Illiterate E Chart No. 1942. Bausch and Lomb Company: Snellen Test Card No. 71-35-93; Illiterate E Test Card No. 71-35-98. (These cost less than 50 cents each.) Charts may be obtained from a medical supply house or from the American Medical Association.

exactly twenty feet from the patient,* and care should be taken to prevent the patient from examining the chart before his test begins. Illumination may be obtained from a 50-watt bulb in an office floor lamp or from a spotlight inserted in a ceiling socket.† Effort should be made to light up the chart evenly and without glare: for more standard illumination a number of commercial illuminators are available. The eye not being tested is covered by a small cardboard square, and care is taken not to put heavy pressure on the eye. Squinting is not allowed. The smallest line of letters which can be read is recorded for each eye.

Part II. Latent Refractive Error (Hypermetropia).—The spectacles containing the plus 1.50 spheres‡ are placed in position and the patient closes both eyes for a few seconds. The left eye is then covered with a card and he is requested to read the 20/20 line. This is repeated with the right eye covered. *Ability to read* the 20/20 line§ through the plus 1.50 spheres with either eye constitutes a failure and indicates that a sizable refractive error is present.

EVALUATION OF RESULTS

The following conditions are indications for referral to an eye specialist, but it should be remembered that the standards for normal visual acuity vary somewhat with the age of the child. It would be well for the individual pediatrician to discuss with the ophthalmologists in his locality what they consider proper standards for referral.

- a. Vision of 20/30 or less in either eye, providing an eye specialist's examination has not been made within the previous twelve months.
- b. Ability to read the 20/20 line§ with either eye through the plus 1.50 spheres.
- c. Symptoms of eye strain, blurred vision, headache, and other conditions which persist and seem to the pediatrician to be significant.
- d. Any significant abnormality noted at the inspection of the *external eye*.

Comment.—Not all children failing these tests will require treatment, but the ophthalmologist should be the one to make this decision. It is not advisable for the pediatrician to indicate to the parents the extent of the eye difficulty, but only to suggest that a further examination by an eye specialist is advisable. This test is a compromise screening device, but represents what present experience would suggest as a practical test. In the near future some very simple apparatus may be available to test for muscle balance. Many devices are on the market and available at present, but none seems completely satisfactory to us at this time: those who wish to use a relatively simple method are referred to our previous reports.^{1, 2, 3}

*Where 20 feet is not available, 10 feet or 15 feet may be used, and the visual acuity scored by the formula: "distance from chart over size of letters read," e.g., 15/50. The number of feet at which each chart line should be read is given on the charts.

†Such as the General Electric "Mazda 150-Watt Projector Spot."

‡Obtainable from any optician on presenting this prescription: R. O. U. + 1.50 sphere. Mount in zylonite spectacles, 40-22-6" skull temples (for larger children) and 38-18-5" skull temples (for smaller children).

§When 15 feet or 10 feet distance is used, ability to read the corresponding line through the plus 1.50 spheres constitutes a failure: e.g. the 10 foot line at 10 feet distance.

SUMMARY

A brief method for examining eyes which requires little time and only a small amount of inexpensive equipment and yet which is efficient in detecting those children, from about the age of 4 through adolescence, who have either diminished *visual acuity* or a *latent refractive error* (hypermetropia), has been described in detail. A supplementation of this test with tests of heterophoria is suggested for those who wish a more complete examination requiring more, but simple, equipment. The necessity for a careful administration of the test because of its brevity and simplicity should be kept in mind.

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ORAL PLASMA FEEDING

A PRELIMINARY REPORT ON NEONATAL FEEDINGS

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THE pediatric investigations that make up this report are based not only upon simple laboratory equipment, but also upon empirical knowledge. This should not surprise the reader, since pediatrics took form in pure empiricism, evolving slowly into a medical specialty, grounded on scientific fact.

The report is presented in the hope that it will be of sufficient interest to engage the attention of investigators in clinics possessing superior laboratory equipment together with a larger choice of subjects and clinical material.

Neonatal weight loss commands the attention of pediatricians, especially with respect to premature infants, and to full-term infants with subnormal weights. More baffling still to inquiry, is the failure of newborn infants to gain after the initial weight loss reaches a plateau.

In the studies of neonatal weight loss, combinations of crude or purified sugars in acid, alkaline, or neutral media were used for prenatal feeding depending on the nature of the experiment itself. Additions of various physiologic salts and proteins were made occasionally to these formulas.

The results of these first experiments were not impressive, as they proved difficult to interpret. It was noted, however, that protein feedings occasionally produced the best weight gains.

Of special interest in this connection was the study by Sanford¹ in 1930, involving 4,622 infants, in a thorough investigation of various complemental feedings used during the neonatal period.

O'Donnel² similarly fed over 1,200 newborn infants with seventeen recognized neonatal formula mixtures. He concluded that it matters little which formula is given, provided it is carefully controlled, and he confirmed at the same time the results of Schorer and Laffoon that hydrating solutions were more conducive to extended breast feeding. O'Donnel noted, however, that those infants to whom he fed the Kugelmass mixture showed an advantage in neonatal weight gain.

Goldman,³ after feeding 102 infants a high protein, low fat, low carbohydrate mixture during the first ten postnatal days, substantiated the opinions of Zahorsky,⁴ Brenneman,⁵ and Marriot and Jeans⁶ that artificially fed infants thrived better on milk formulas high in protein than on standard nursery feedings.

These results, as well as mine, pointed to the value of incorporating proteins in some form or other, in neonatal and complemental feedings, as the best feeding to remedy neonatal weight loss. Further experimental neonatal feedings were obviously unnecessary, but I found at this point of my observations, a pertinent article by DeMarsh.⁷

From the Departments of Medicine and Cardiology of the Good Samaritan Hospital.

He pleaded both for the salvaging of all available placental blood as the best possible start for the newborn, and for the delayed clamping of the umbilical cord. In the same article he quoted Schiff⁸ in finding: "... an increased excretion of nitrogen in infants, whose cords were cut early; and concluding that the placental blood acted as a source of nourishment protecting infants against the breakdown of body protein. . ."

This opinion led me to study the physical changes occurring in the cord after delivery, since it has often been observed that premature infants and infants delivered with collapsed cords, or following prolonged labors, show relatively greater neonatal weight loss and hold the initial weight loss plateau longer.

Approaching the problem from this direction, I now placed an infant, as soon as possible after delivery, on a level with the maternal buttocks. I then made a scissor-cut into an umbilical vein of the infant, and inserted therein, a self-retaining cannula.* This venous cannula was connected to a water manometer† and the subsequent manometric readings were recorded.

The readings obtained for a number of cases showed that when the cord pressure was high, the initial weight loss was less. The procedure as a whole was so complicated by little known variables in the maternal structures, in the infant, and in the placental blood as a colloidal medium that it was abandoned.

It indicated, nevertheless, that a continuous transfusion of plasma solution, via the cord, was possible for a short period of time, at least; and that the method might be of value in sustaining the newborn infant, especially the premature infant, over a most hazardous period of his adjustment.

This method was adopted as occasion arose, and, while practicable, its supervision entailed some difficulty that grew proportionately with the prematurity of the infant.

The results were of value in a few cases; at least there were no deaths.

About this time Noon⁹ read a paper in which he compared various complementary feedings during the first two weeks of life of the newborn infant. The formulas discussed constituted the pediatrician's armamentarium with a few exceptions.

Noon through photographic slides showed comparisons in the following respects: the initial weight loss, the plateau, and the gradual return to birth weight. These points, familiar to pediatricians, led Burkett⁹ to reaffirm the belief that: "... The initial weight loss of the newborn is a natural phenomenon which closely coincides with the duration of the flow of colostrum. . ."

Before describing the following intensive study of the events subsequent to delivery of some infants, allow me to raise a question. Why does Nature provide as early as the fourth month of pregnancy, a substance called *colostrum*, marvellously adapted, in any eventuality, to all critical needs of the coming newborn infant, yet offered to it for a period of only forty-eight hours after delivery?

*Beckton-Dickson: Special Needle G-18 483LNR.

†Beckton-Dickson: Direct Venous Pressure Apparatus.

To put it another way, let us say that Nature provides highly specialized colostrum, at the earliest possible time to meet the exigencies of extra-uterine life. She cherishes and conserves it, so to speak, while holding in abeyance for a period of forty-eight hours after delivery the lactogenic forces of parturition, which in other mammals are concomitant with parturition.

It would appear, therefore, that human milk is not Nature's first food substance of predilection for the human newborn infant, for as we have seen, the human breasts provide first and foremost, colostrum. In this respect, woman differs radically from all other mammals, who invariably possess milk in their mammary glands in the first few hours of delivery, or even during the process of labor.

A striking fact stands out in this connection. The closest available substance corresponding to colostrum is human plasma, provided the fat content be removed. To quote available literature further on the subject is disappointing for the reason that studies on the subject of colostrum are in need of revision. The libraries offer little material beyond the recopied statements of textbooks regarding its physical properties.

Medical authorities agree on one point, namely, that the fat of the colostrum is not desirable, and in some instances, baneful.¹⁰ Three additional facts stand out from existing literature on the subject: (1) Colostrum, although containing fatlike globules, nevertheless resembles plasma more closely than human milk.¹¹ (2) Plasma is a transudate. (3) The intestinal wall within the newborn infant is readily permeable to protein, and to allied substances, the permeability decreasing in direct proportion to the maturity of the infant.¹²⁻¹⁶

As regards current medical literature on the subject of the absorption of colostrum, there seemed an utter absence of it in the libraries within reach. The closest approach to it, to which attention is called, is an excellent work, by Höber,¹⁷ who described some important researches of a colleague, von Möllendorf^{18, 19} of Kiel, in Germany.

Von Möllendorf¹⁸⁻¹⁹ found that in newborn mice, trypan blue which normally passes body membranes very slowly (probably through phagocytes), and casein (which normally must be digested, before it can be absorbed), penetrated the intestinal epithelium quite rapidly, and that both substances promptly appeared on the other side of the epithelium after being put into the intestine.

This unique diffusion coincided with the absence of intestinal juice. When the juice appeared, the mature type of permeability was established.

These experiments and their noted results, unrelated as they are to oral plasma feeding, nevertheless led me to conclude that no harm could possibly arise from substituting plasma for colostrum.

With this in mind, seven premature infants were fed *orally* with a plasma solution in place of any other nutrient substance, adding after twenty-four hours of this feeding, plasma to the variously constituted neonatal feedings. The object was to reduce the limitations set by employing merely one or two types of neonatal feedings.

In all cases neonatal weight loss ceased, and the infants thrived. All moreover showed appreciable weight losses when the plasma was subtracted from the feedings (Chart 1). These changes were more conspicuous than those observed in other types of neonatal feedings of high protein content.

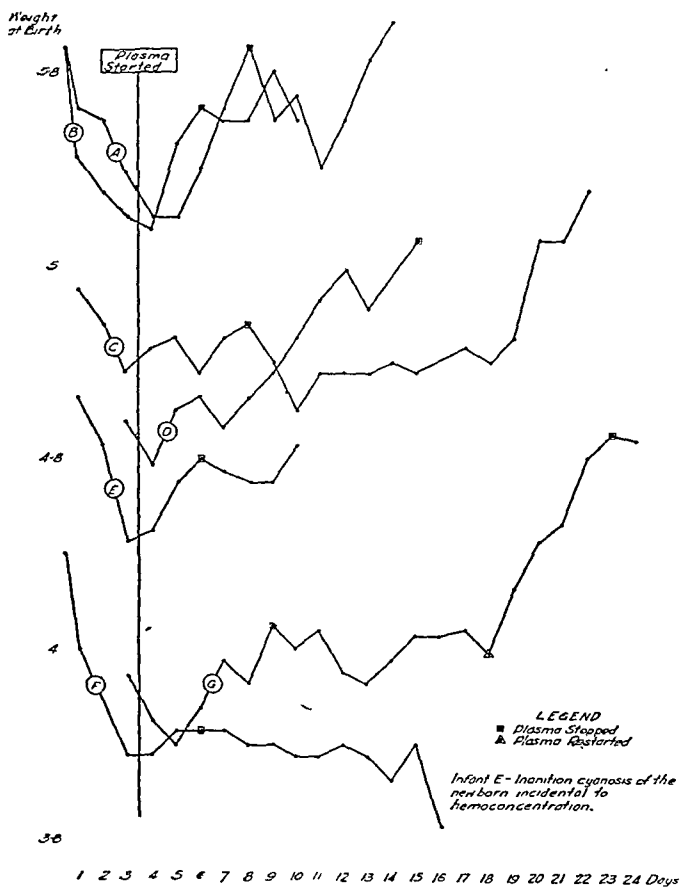


Chart 1.

While these experiments were being performed on individual premature infants, the possibility of coincidence, accidental or otherwise, arose to challenge the interpretation of results and the entire investigation was imperiled by this question, when fortunately a set of identical 8-month, premature female twins became available for study.

Case 1.—The first of the twins, Infant A (Chart 2), subjected to the traumas of birth, was fed plasma solution orally. The second, Infant B (Chart 2), delivered easily as a vertex, was fed only honey-water solution, according to the directions of Schlutz and Knott.²⁰

Infant B exhibited, within twenty-four hours, the picture of a moribund premature infant, so well-described by Curtin²¹ as *shock*. I prefer in this

connection, however, the definition, "Inanition cyanosis of the newborn incidental to hemoconcentration."

In spite of constant inhalation-oxygen therapy, the infant remained cyanotic for sixteen hours.

At this point the method of feeding was reversed; Infant B receiving plasma orally, while Infant A received only honey-water. Within one hour,

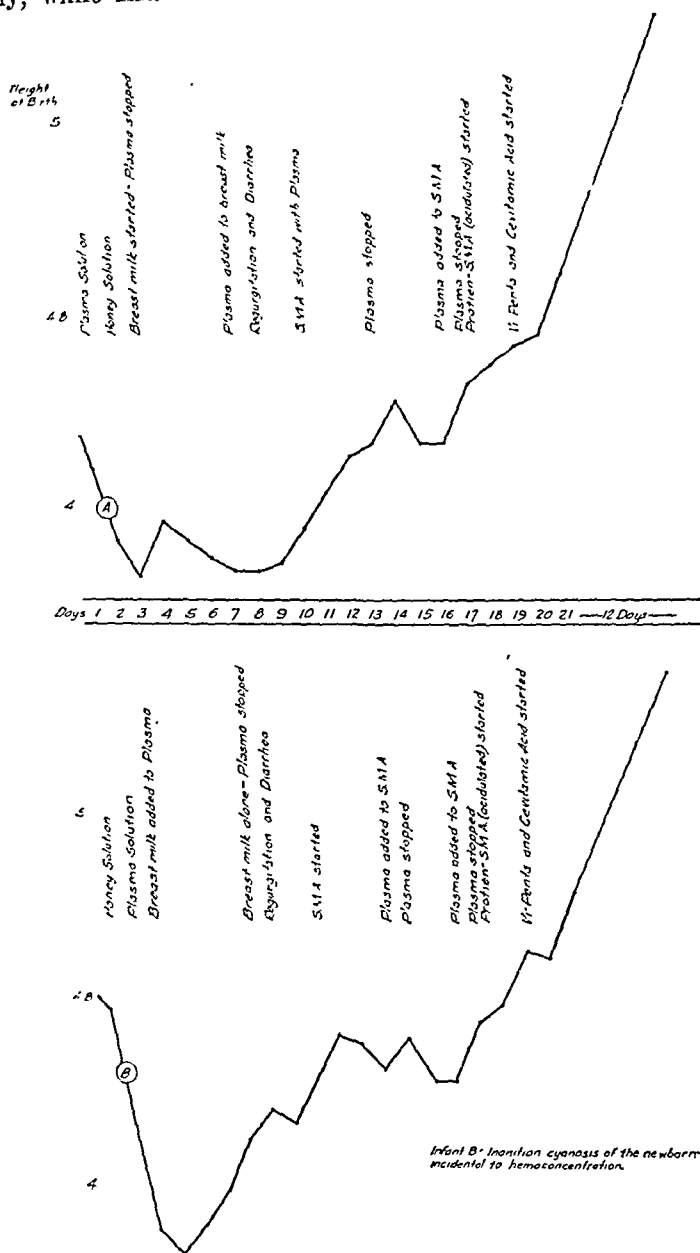


Chart 2.

Infant B became less cyanotic and more active. She cried feebly, and made a genuine attempt to nurse from the nipple; respirations became slower and deeper, permitting, within four hours, the oxygen to be discontinued permanently.

Curtin²¹ comments on the startling results in marantic infants when plasma was administered intraperitoneally. Plasma was continued until the mother was able to produce breast milk. This was obtained through a breast pump,* both breasts being emptied simultaneously through a Y tube connecting bilateral nipple cups, an improved and timesaving device, producing the best possible yield with the least waste.

Infant B was fed breast milk and plasma: Infant A, breast milk alone. Infant B, in spite of her precarious condition on the previous day, showed the advantage immediately.

The mother's milk supply failing at this time, milk from a second mother was obtained. This mother had eaten heavily of fish two hours previous to the pumping of the breasts. Both infants responded with regurgitation and diarrhea. Vomiting was seldom observed during plasma feeding, but in spite of its occurrence here, the fact remains that Infant A, fed on plasma and borrowed breast milk, thrived better than Infant B, fed on borrowed breast milk alone.

The infants were then fed S. M. A.† as follows: Infant A was fed an S. M. A.-plasma mixture, while Infant B was fed S. M. A. alone. Infant A continued to gain weight, while Infant B lost weight. The feeding formulas were then reversed, with the results obtained shown on Chart 2.

Because of a shortage of plasma at this time, the infants were placed on protein-S. M. A. (acidulated) alone, and having reached birth weight, their feedings were augmented with vitamins A, B, C, and D, all purposely omitted up to this time. Results subsequent to the feedings are shown in detail on Chart 2.

Case 2.—Altering the procedure somewhat, it was applied to a set of identical male twins as follows: Infant A was fed plasma in honey solution. Infant B was fed honey solution alone.

On the following afternoon both infants were started on breast milk, but to Infant A's feeding, plasma was added. The breast milk supply becoming deficient on the next day, S. M. A. feedings were substituted for three feedings, with plasma added to Infant A's feedings; breast milk thereafter was fed to both infants.

Infant A, accordingly, on each successive feeding received plasma-breast milk, while Infant B received breast milk alone. Chart 3, shows the result. Particular attention is called to the fact that Infant A, the first-born of the twins, who was subjected to the traumas of labor, and who weighed less than Infant B, received plasma, gaining as a result, 8¼ ounces over birth weight.

*Dr. Abt Improved Electric Breast Pump, Bodine Electric Company, Chicago, Ill.

†S. M. A. Corporation, Cleveland, Ohio.

The initial weight loss of the plasma-fed Infant A, moreover, was only 2 ounces over a twenty-four-hour period; whereas the initial weight loss of Infant B, who received no plasma was $5\frac{3}{4}$ ounces over a ninety-six-hour period.

Infant A, fed on plasma, recovered his birth weight in two days, while Infant B, who received no plasma, required eleven days to regain birth weight. Or more clearly, infant A, who was fed plasma and breast milk, gained $8\frac{1}{4}$ ounces, while Infant B, who was fed breast milk alone, gained but $2\frac{1}{2}$ ounces over the thirteen-day feeding experiment.

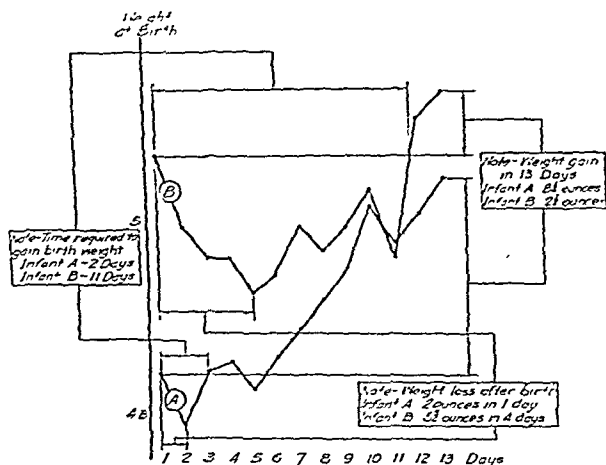


Chart 3.

Case 3.—More recently I investigated the feeding of a set of twins, who failed consistently to gain weight over a period of twelve days. These twins were the heterogeneous type. The mother suffered a serious post-partum hemorrhage that precluded the feeding of breast milk directly or indirectly, in consequence of which the infants were fed a cow's milk and dextrimaltose mixture.

At my suggestion, this mixture was altered to an evaporated milk and dextrimaltose formula, in the hope that the increase in caloric feeding would prove beneficial, but the weight gains remained slight until plasma was added.

Chart 4 shows the result of plasma feeding, twelve days after the respective infant body weights had remained stationary. In this case, note that the amount of evaporated milk fed *per diem* during the plasma feeding was purposely reduced.

In spite of the reduced milk feeding, Infant A gained $8\frac{3}{4}$ ounces during the first four days of plasma feeding in contrast to losing $3\frac{1}{2}$ ounces during the preceding twelve days. In much the same way, Infant B gained 9 ounces during the four-day plasma feeding, and only 5 ounces during the preceding twelve days.

A striking fact recorded at this point, was that in every feeding experiment carried out on the infants, the addition of plasma to the various formulas

described eliminated vomiting; and that the omission of plasma, on the other hand, predisposed to vomiting. The entry for the last day on Chart 4 and Case 7, further illustrates this condition.

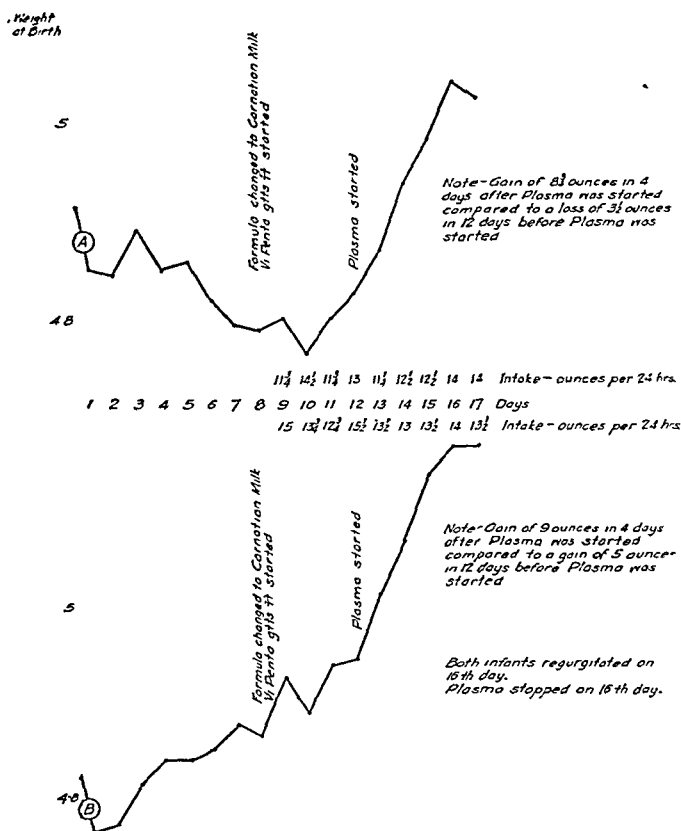


Chart 4.

Case 4.—(An 8-month premature girl.) The mother was placed in the charge of a colleague of mine about the time of her sixth month of pregnancy. She had gained 15 pounds in the preceding two weeks, became edematous, and suffered with severe headache and dizziness.

Her clinical laboratory report at the time showed: blood pressure, 180-100-90; specific gravity of urine, 1020; albumin in urine, 4 plus.

In spite of careful regulation under excellent medical and nursing supervision the condition worsened until the day of her eighth month of pregnancy, at which time immediate hospitalization was advised.

Almost upon admission, the woman fell into spontaneous labor, and was subsequently easily delivered, after episiotomy, with low forceps.

The infant was fed plasma with breast milk, at first borrowed, for a period of a week, at the expiration of which time, she appeared capable and

vigorous enough to nurse at the breasts of the mother. The infant failed to gain weight, while the breasts of the mother grew flabby and unproductive.

An S. M. A. mixture was fed to the infant and apparently was well tolerated, but again the weight gain was slight until plasma was added (Chart 5).

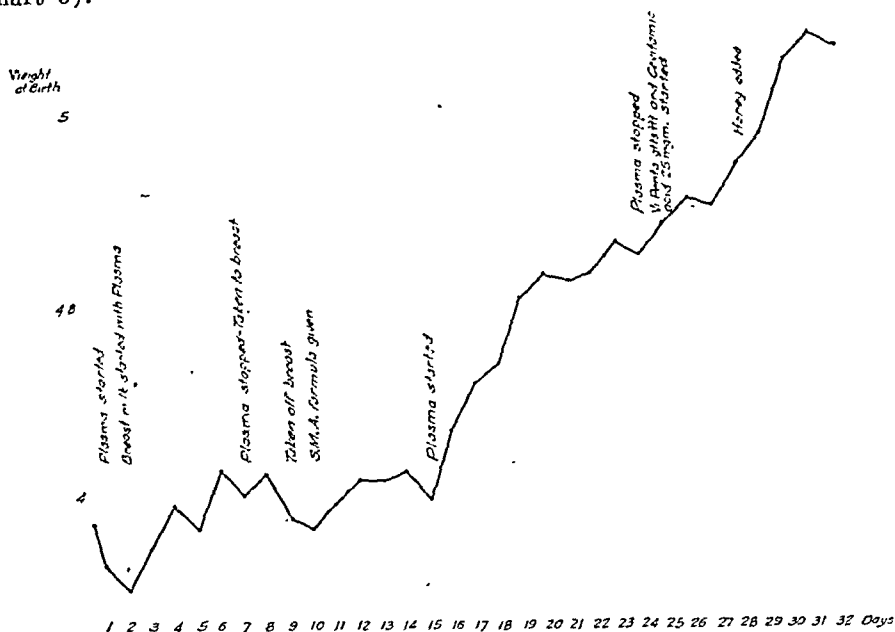


Chart 5.

Up to this time I had dealt with premature infants; with but little effort to determine and standardize the amount of plasma obviously essential to sustain life in premature infants. Throughout the course of the initial experiments, plasma was sparingly and even meticulously administered. With plasma more freely given, however, neonatal weight loss became almost negligible.

In the opening paragraphs attention was called to the studies of prominent pediatricians, repeatedly demonstrating that neonatal weight loss, especially in premature infants, could not ordinarily be averted. I felt, however, that if in spite of all evidence to the contrary I could prevent neonatal weight loss by the use of plasma, this baffling problem would be solved.

Using as a basis the absence of neonatal weight loss, the absence of gastrointestinal intolerance, and the general behavior of the newborn premature infant as indicators, I found on these premises that 10 c.c. per kilogram, administered every two hours, was approximately sufficient for all cases under investigation.

If the weight gain remained stationary or increased after the first twenty-four hours, the feedings were given every two and one-half hours. After forty-eight hours, the feedings were given every three hours.

Milk feedings were withheld for forty-eight hours, the plasma being administered during this interim in equal amounts of hydrated solution, my own preference being a honey solution.²⁰

Chart 5A shows a typical premature infant (Case A) contrasted with two casually selected hospital premature infants (B and C), not fed with plasma. Premature Infant A behaved much like any full-term infant. The cry was lusty, movements vigorous and coordinated, color rose-pink, and skin turgor healthy and supple.

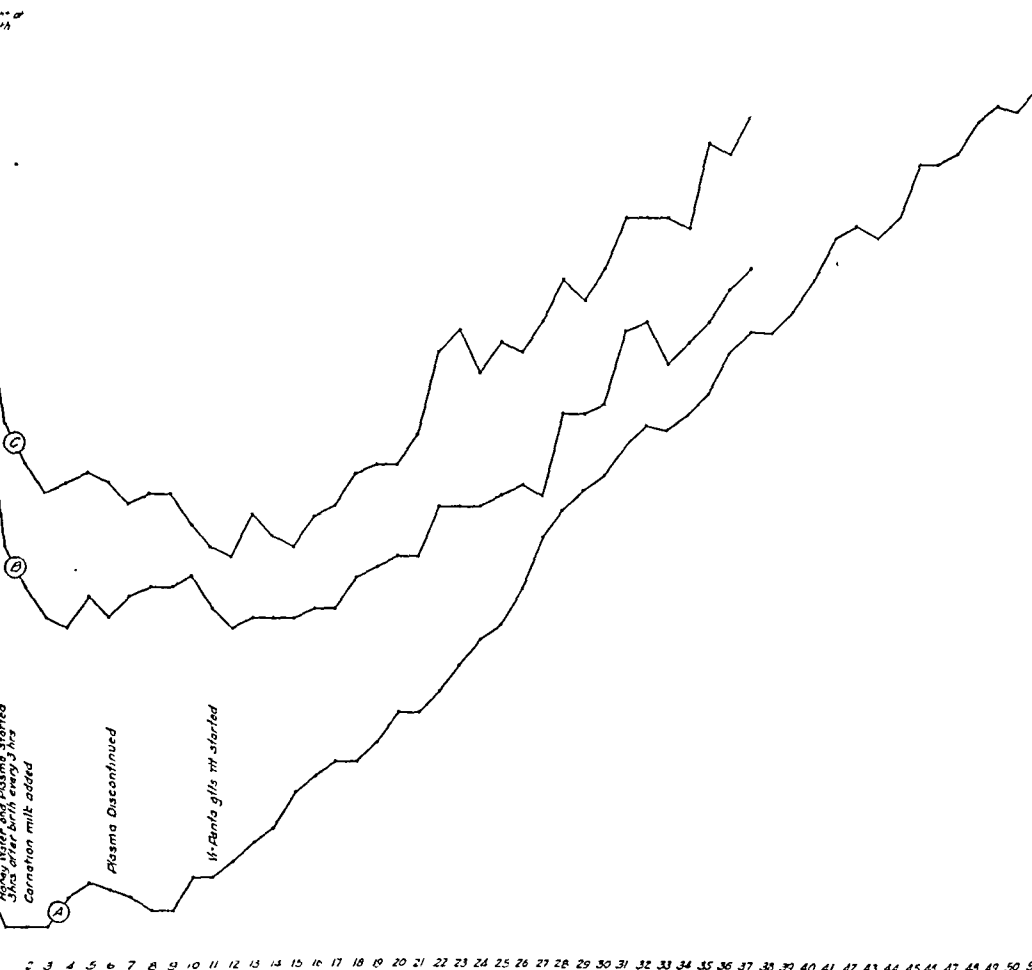


Chart 5A.

The doubtful "forced feeding" method of many present-day specialists, was in this case never attempted. It was observed, at the same time, that incubator life of the first ninety-six hours was entirely normal; and that it was subsequently transferred to an overcrowded nursery along with other full-term infants, to be treated as such.

It occurred to me at this point that the results of these investigations, however meager, performed on essentially normal premature infants, might be applied to certain abnormal infants encountered in pediatric practice.

Case 5.—The first of these encountered was a full-term infant, delivered after active labor for thirty hours of a primipara with a representative typical male pelvis.

The infant was in the R.O.P. position, the head abnormally flexed and molded. Upon delivery with low forceps after episiotomy, the infant refused to breathe. The umbilical cord was collapsed and pulseless. Heart sounds were feebly heard, the rate being only 30 to 40 per minute.

Conventional means, including oxygen therapy by resucitator, were taken to revive the infant. Alpha-lobelin (1 ampule), with epinephrine (2 minims), was administered, since collapse seemed imminent.

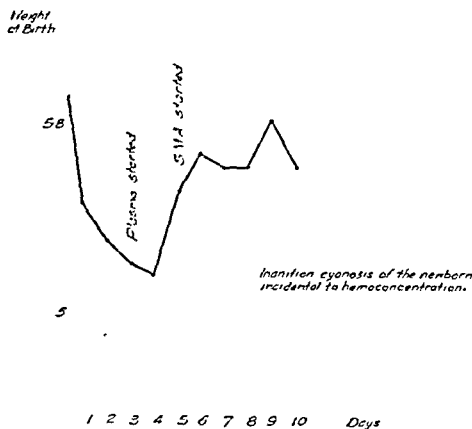


Chart 6.

After thirty-six hours of effort, including almost constant therapy of oxygen inhalation, the infant showed little improvement; in fact, the infant suffered generalized rigidity with a temperature of 100° F. and became, in addition, dehydrated, and acidotic, refused all feeding, and regurgitated even gavage feedings.

In this critical condition, plasma was administered orally to the infant and retained. Within an hour a profound change was observed. The infant's respirations decreased in number and improved in depth. The cyanosis disappeared, with the need for further oxygenation rendered unnecessary. The rigidity likewise disappeared, regurgitation ceased, and the temperature receded to 98.4° F. as the day passed. The infant, moreover, slept soundly between feedings.

Curtin²¹ noted a similar effect when he treated infants intraperitoneally with plasma. Twenty-four hours later, the child under observation breathed normally, cried vigorously, and seemed hungry; in fact, the child appeared as a healthy newborn infant, with the exception of the stigmas of molding.

In this case, the plasma supply failed, and feeding with S. M. A. alone, was started (Chart 6).

Case 6.—My attention was now directed to a first-born male infant, nearly 2 months old. His birth weight was 6 pounds, 4 ounces, falling after ten days to 5 pounds, 13 ounces. While in the hospital he made feeble attempts to nurse at the breast, and was in consequence offered an evaporated milk-Karo formula, tolerating it well, and gaining in weight.

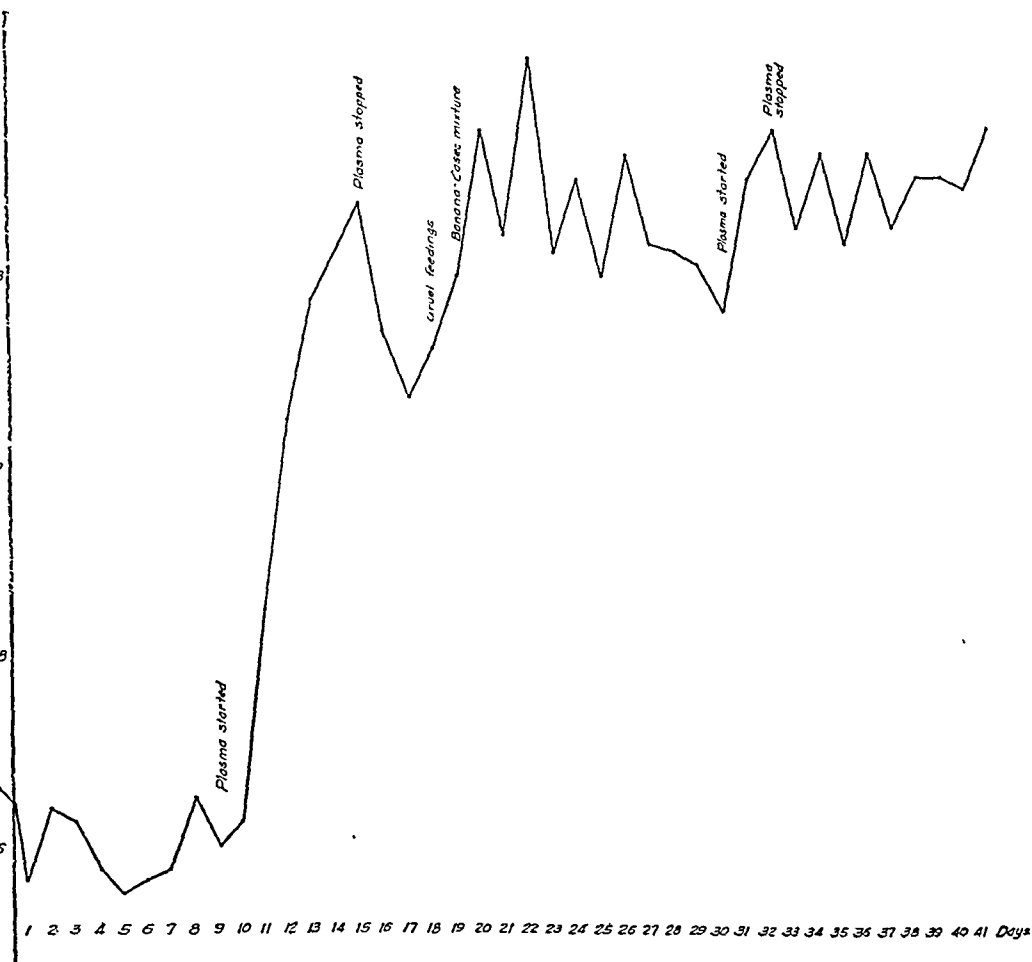


Chart 7.

Upon discharge from the hospital, however, the infant failed to retain for any length of time, any of several kinds of feedings. Revisions were made in the various mixtures over a period of six weeks at the child's home. The parents, however, being none too intelligent nor cooperative, the infant was returned to the hospital where better supervision was afforded.

Upon the infant's readmission, at which time I was first consulted, although his age was nearly 2 months, his weight was only 6 pounds, 13¼ ounces.

A tentative diagnosis was made of an atypical pyloric stenosis. Belladonna-phenobarbital treatment was instituted without results.

With the feeding of plasma orally to this infant, the weight gain was remarkable (Chart 7); when the plasma feeding was interrupted, the infant lost weight but regained it upon resumption of the plasma feeding. Gruel feedings were attempted with some success, but at this point, the none-too-intelligent father signed the infant's release.

The infant was subsequently readmitted to the hospital and operated upon, according to the Ramstedt method, and at which time, a pyloric stenosis, which resulted in a nearly complete atresia was corrected.

Case 7.—Another male infant, of Jewish parents, was of subnormal weight and, in spite of careful adjustment of an evaporated milk formula, continued to lose weight steadily. With the approach of the eighth day for circumcision, the attending physician feared the rite to be detrimental to the infant's physical condition.

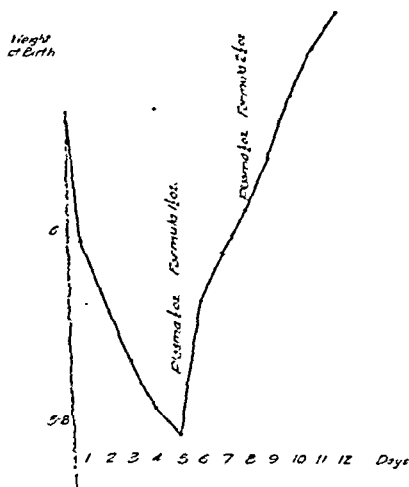


Chart 8.

Following a consultation on the case, he was placed on an evaporated milk formula, unchanged except for the addition of plasma. Upon the first feeding of the plasma addition, the infant, who had vomited consistently for five days, ceased to vomit without relapse.

The entire picture of the infant's condition was redrawn within the ensuing twenty-four hours, with the body color changing from a waxy pallor to a ruddy pink and with respirations deeper and slower.

In the next twenty-four-hour cycle, the infant exhibited even more improvement, by becoming hungry, sleeping between feedings, and gaining steadily in weight.

The rite of circumcision finally was performed, without harmful effect to the child and without subsequent loss of weight.

Chart 8 further describes the subsequent history of this case.

SUMMARY

1. Human plasma has been successfully administered by mouth to premature and neonatal infants with satisfactory results. So far as is known from available literature this is the first time plasma has been administered orally.

2. Reduced vomiting would indicate the absence of gastric irritation in this kind of feeding. It is not unlikely that plasma may act as a natural antacid in such feeding to reduce vomiting (Case 7).²²

3. Intestinal disturbance was likewise absent if the plasma when fed to infants was free of red cells and of suspicious antigens.

4. The fact that Nature's first nutrient substance is comparable in many respects to orally fed plasma solution, provided recognized and undesirable elements are absent, largely removes any natural and scientific disagreement from the idea of high protein neonatal feedings.

5. It is possible that hormones, such as estrogenic substances, vitamins, and immune material, could prove an added benefit to the newborn infant in this type of feeding.

6. It remains a problem for further intensive study to show whether human plasma could be replaced in this form of "intestinal transfusion" by a synthetic protein-salt-carbohydrate mixture, in which the protein substance is not of human origin.

7. The use of autogenic protein may be more beneficial to the newborn infant, whose capacity for antibody production is much smaller than in later periods of life.

8. Weight gain is not necessarily to be associated with the complex picture of plasma protein digestion, but rather with the ready absorption of plasma protein, a fact borne out by the single case (Case 6) in which an operation removed a pathologic obstruction.

The cyanotic syndrome encountered in premature and neonatal infants, and which here *faute de mieux*, I call "the inanition cyanosis of the newborn incidental to hemoconcentration" has been successfully treated on three different occasions by the oral administration of plasma.

CONCLUSIONS

In the light of the foregoing investigations, and in the continued success of neonatal, oral administration of human plasma, I am convinced that whatever type of neonatal feeding we shall adopt eventually, it will be higher in protein than are the customary neonatal feedings of today.

This protein feeding, moreover, will be derived from plasma, to be substituted by synthetic proteins only, should human plasma be, at the time in question, unavailable.

It may well be that such synthetic proteins will prove inferior by reason of the absence of valuable and cryptic substances awaiting isolation in human plasma.

The merits gained through these investigations compel pediatricians to insist on early colostrum and breast feedings, since an added benefit is obvious with higher protein neonatal feedings.

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THE USE OF GENTIAN VIOLET IN CHILDREN INFECTED WITH *ASCARIS LUMBRICOIDES*

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THE work of Wright, Brady, and Bozicevich¹³ and of D'Antoni and Sawitz⁴ has demonstrated that gentian violet is unquestionably the drug of choice in the treatment of infections of the pinworm, *Enterobius vermicularis*. It has been given to thousands of infected persons without a recorded fatality. The drug is administered three times a day before meals and has been given for from ten to thirty consecutive days. Nausea, vomiting, abdominal pain, lassitude, and diarrhea occasionally follow the administration of repeated daily oral doses of gentian violet, but these reactions quickly subside when the dosage of the drug is decreased or is discontinued for a day or two.

According to Wright and Brady¹⁴ "contraindications for the use of gentian violet include concomitant infestations with *Ascaris lumbricoides*, moderate to severe cardiac, hepatic or renal disease, alcohol and diseases of the gastrointestinal tract." Unquestionably these workers were wise in suggesting contraindications to the use of gentian violet until the toxicity of the drug in man could be more thoroughly studied. However, they give no experimental evidence and the literature does not point definitely to the production of obstruction or the migration of *Ascaris* by gentian violet or an enhanced toxicity of gentian violet when *A. lumbricoides* is present, and the subject therefore seems to justify further exploration. This is particularly indicated, in view of the fact that gentian violet was first used by DeLangen⁵ against *Strongyloides stercoralis* which invades the intestinal mucosa, and Faust and Yao⁶ began its use in *Clonorchis sinensis* infections which may produce marked alterations in the liver of man. The course of therapy in *Clonorchis* infections may be two to three times as long as that recommended for *Enterobius*.

If gentian violet is irritating to *Ascaris* and thereby causes serious complications, its routine use in pinworm infections without first eliminating the *Ascaris* present might be dangerous. A routine frequently followed is to treat for pinworm on the basis of a positive N. I. H. cellophane swab (or an adult worm found on the stool by the patient) which seldom detects the presence of *Ascaris*. According to this warning an examination of the stool for *Ascaris* and its treatment if found is imperative.

It is known, of course, that carbon tetrachloride when given to *Ascaris* infected persons may cause the worms to migrate or entwine themselves together and produce intestinal obstruction (Lamson, Minot, and Robbins.¹⁰ Until this appears not to happen in the case of gentian violet, it should be given consideration in the use of that drug in the presence of *Ascaris*. The chemical constitution

of gentian violet is, however, so different from that of carbon tetrachloride that it would be surprising if their action on *Ascaris* were similar.

Kouri, Sellek, and Rivera⁷ reported treatment with gentian violet of two children who harbored both *Strongyloides stercoralis* and *A. lumbricoides* and noted no evidence of the migration of *Ascaris* or of intestinal obstruction due to them. The children were 8 and 12 years old and were given 100 mg. of gentian violet daily for ten consecutive days. The 12-year-old child was later given an additional five-day course of gentian violet.

On questioning physicians practicing in the mountainous areas of our southeastern states as well as one in the tropics where both *Ascaris* and *Enterobius* are often found to be present in the same individual, I learn that they have been treating pinworm with gentian violet without first ascertaining whether or not *Ascaris* is present and eliminating it. They have noted no untoward reactions. In one mountainous area where I recently found 60 per cent of the children in one school infected with *Ascaris*, a local physician has never seen a case of obstruction due to *Ascaris* despite the fact that it is his custom in this area to treat children with gentian violet for pinworm.

To test the possible stimulating effect of gentian violet upon *Ascaris* a number of live *A. lumbricoides* were secured from pigs at a slaughter house and immersed in varying concentrations of gentian violet in salt solution. The worms were maintained at 35° C. and observed for two hours. (Table I.)

TABLE I. ACTIVITY OF *ASCARIS LUMBRICOIDES* (FROM SWINE) IN GENTIAN VIOLET SOLUTIONS

GENTIAN VIOLET CONCENTRATION	WORMS	TIME IN GENTIAN VIOLET AT 35° C. (HR.)	ACTIVITY
1 to 1,000	4	2	Slightly more active than controls?
1 to 10,000	4	2	Same as controls
1 to 20,000	4	2	Same as controls
1 to 50,000	4	2	Same as controls
1 to 100,000	4	2	Same as controls
Controls	4	2	Same as controls

It will be noted in Table I that the gentian violet solutions did not stimulate the worms to especial activity and did not result in their clumping together. The worms in the 1 to 1000 gentian violet solutions were perhaps slightly more active than the controls, the difference in activity, if any, however, was not marked.

In light of the findings in Table I and in view of the failure of the gentian violet to stimulate *Ascaris* to migrate or cause obstruction in patients treated for *Strongyloides* or pinworm and since three out of four *Ascaris* infected dogs treated with this drug passed part or all of their worms, it was deemed safe and worth while to test it on *Ascaris* infected children.

Twenty children harboring *A. lumbricoides* were given gentian violet by mouth two or three times a day for ten consecutive days. (Table II). The usual gentian violet daily dosage for pinworm (10 mg. per year of age) was followed as closely as the 32 mg. pills would permit. Children 8 years of age or younger were given 2 pills of 32 mg. gentian violet daily and children of 9

years of age and older were given 3 such pills. The pills were "Seal-Ins" timed to break up in four and one-half hours and were taken from one-half to one hour before meals. Stools were collected from time to time to check the presence of the gentian violet in them and the children were questioned daily for evidence of toxicity of the drug.

There was no evidence that the *Ascaris* were stimulated by the gentian violet. No worms migrated out of the mouth or anus and there was no evidence of intestinal obstruction by them. Only two children complained of abdominal pain. It occurred in both on the sixth and seventh day of treatment. The pain in one child was deemed sufficient for the drug to be discontinued for the seventh day of treatment, the other child continued treatment. The abdominal pain disappeared in both and was probably caused by the gentian violet, as such distress is encountered in persons taking gentian violet who are not infected with *Ascaris*. Two children became nauseated but did not vomit. A daily check was made on the number of stools passed by each child. In general the number increased slightly during treatment and there was a tendency toward looseness. The absence of vomiting, abdominal distention, and the presence of several daily bowel movements definitely rules out intestinal obstruction by the *Ascaris* in the treated children.

The stools of the children treated with gentian violet were all egg-counted by the Stoll and Hausheer¹¹ technique before treatment and one week after the completion of the ten-day treatment with gentian violet. Results are shown in

TABLE II. ADMINISTRATION OF GENTIAN VIOLET TO CHILDREN INFECTED WITH ASCARIS LUMBRICOIDES—"SEAL-INS" PILLS GIVEN FOR TEN CONSECUTIVE DAYS

NO.	AGE	WT.	DOSE MG. DAILY	EGG COUNT 0.075 C.C.		TOXICITY
				BEFORE TREATMENT	AFTER TREATMENT	
1	12	114	96	4,300	0	None
2	13	104	96	26,500	28,000	None
3	12	96	96	1,400	20,500	None
4	12	90	96	27,600	19,900	None
5	10	80	96	2,600	3,000	None
6	10	80	96	1,000	0	Abdominal pain sixth and seventh days of treatment
7	12	80	96	1,600	200	Nausea
8	10	76	96	8,400	5,900	None
9	11	74	96	14,000	0	Nausea
10	10	70	96	1,900	300	None
11	11	70	96	5,900	18,500	Abdominal distress sixth and seventh days of treatment; no drug given on seventh day
12	11	68	96	2,300	7,800	None
13	9	68	96	900	2,200	None
14	9	68	96	500	0	None
15	11	66	96	75,700	35,400	None
16	7	60	64	15,200	4,800	None
17	8	60	64	80,400	39,400	None
18	8	56	64	24,600	6,700	None
19	7	50	64	8,500	500	None
20	8	50	64	5,000	700	None
Total				308,000	193,800	

Table II. It will be noted that four of the infected children lost all of their worms during treatment and that the total egg count of the group fell from 308,300 to 193,800 per cubic centimeter of feces, a reduction of 37 per cent. On the basis of this study gentian violet cannot be classed as an effective ascaricide, although it appears to have some activity against this parasite.

DISCUSSION

The failure of routine gentian violet pinworm therapy to stimulate *A. lumbricoides* to migrate or produce intestinal or pharyngeal obstruction in twenty treated children indicates that this drug is not specifically irritating to the worm. It is possible, however, that if large numbers of *Ascaris* infected individuals were given gentian violet, that instances of migration or obstruction by the worms might be encountered. Such was reported by Lambert⁹ to be the case in *Ascaris* infected persons treated with carbon tetrachloride. Lamson, Minot, and Robbins¹⁰ also reported several instances of *Ascaris* migration and pharyngeal and intestinal obstruction following the administration of carbon tetrachloride. On the other hand many persons infected with *Ascaris* have been given carbon tetrachloride without untoward results.⁸ The chemical constitution of gentian violet, a methylrosaniline, is very different from that of carbon tetrachloride, a halogenated hydrocarbon, and there seems no more reason to suspect gentian violet of this "stimulating" property than the many sulfonamide compounds which are given without a thought of *Ascaris* complications.

Migration of *Ascaris* and obstruction occurs occasionally in so-called normal children infected with *Ascaris* and perhaps more commonly in persons with fever.³ Watkins and Moss¹² reported two cases of acute intestinal obstruction in children before and following treatment with the time honored *Ascaris* remedy, santonin.

It is recognized that an individual infected with *Ascaris* and with pinworms should have both parasites eliminated. Since the treatment of the *Ascaris* infection can readily be accomplished with hexylresorcinol ("Crystoids" Anthelmintic) and as some of the *Enterobius* will likewise be eliminated at the same time, it is suggested that this treatment precede the gentian violet treatment aimed specifically at *Enterobius*.^{1, 2}

SUMMARY

1. Gentian violet therapy for ten consecutive days did not produce findings suggestive of migration of *A. lumbricoides* or in intestinal or pharyngeal obstruction in twenty treated children. It appears, therefore, that gentian violet is not a specific irritant to *Ascaris*.

2. A 37 per cent reduction in the *Ascaris* egg count following gentian violet therapy suggests that this substance is slightly effective against *Ascaris*.

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TOXOPLASMOSIS IN A LARGE MINNESOTA FAMILY

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IT WAS found by Wolf, Cowen, and Paige in 1939¹ that a protozoan of the genus *Toxoplasma*, long known to be pathogenic for certain lower animals, can also infect man, producing the disease, toxoplasmosis. In man the infection can be either congenital or acquired. The most common signs in the congenital form are hydrocephalus, microcephalus, chorioretinitis, cerebral calcification (demonstrable by roentgenogram), and psychomotor disturbances, especially convulsions. The acquired disease usually produces the symptoms of an acute encephalitis, or more rarely an atypical pneumonia with a generalized maculopapular skin eruption. Since 1939 thirty-odd human cases of toxoplasmosis have been reported.¹⁻¹⁰ However, at the present time little is known regarding the epidemiology of the disease. Therefore, case reports with special studies relating to the circumstances under which the disease makes its appearance should continue to be of value.

Reports in the literature indicate that mothers of infants with toxoplasmosis usually have demonstrable antibodies against the toxoplasma organism in their blood. However, extensive investigations of such families have not been reported. Obviously, knowledge concerning the entire family of each proved case would be of great importance in determining the infectivity rate and the range of variation in symptomatology in such cases.

We were fortunate in having the opportunity to study a typical case in a 14-year-old girl who was a member of a large Minnesota family. The patient had ten living siblings and five other close relatives, all of whom were very cooperative. Complete physical studies, including funduscopic examinations, were made on eleven members of the family. Neutralization tests against the toxoplasma organism were done on blood serum from these and four other members of the family group. Two siblings of our patient could not be studied as one was in the Army overseas and the other died at birth with an enlarged head. The latter sibling might have suffered from hydrocephalus due to toxoplasmosis occurring in utero, a condition not infrequently referred to in the literature.³ Since no post-mortem examination was made, however, this cannot be listed as a proved case.

CASE REPORT

C. G. was a 14-year-old white female, the sixth of twelve children born of two seemingly normal adults of German extraction. She had complained of nervous headaches since she was a small child. At 12 years of age she first complained of transitory spots before her eyes unassociated with any particular activity. Coincidentally, she began to have occasional pain in the right eye, heard noises in the right ear, and suffered from attacks of

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nosebleed every three or four weeks. Nine months before admission to the hospital, the headaches became more severe and were described as "migraine-like" by the patient. They occurred one or two times monthly and were frequently accompanied by vomiting. At times she became somewhat lethargic and frequently slept from three to four hours during the day.

Although the patient was said to have been born one month prematurely, her birth weight was seven pounds. She was bottle fed. She received cod-liver oil but no orange juice. She walked at 10 months of age and said words at 17 months. When the patient was in the fourth grade at school, the school physician informed the mother that she had no central vision in the right eye. In spite of this poor vision, however, the child did very well in school, receiving high grades until the severity of her attacks of headache required her to stay at home.

At the time of her admission to the hospital, physical examination showed her to be a fairly well-developed, well-nourished, cooperative, intelligent, 14-year-old white female who did not appear acutely ill. The head was 56 cm. in circumference, a normal measurement for her age. The body temperature was 98° F.; pulse, 96; respirations, 22; and blood pressure, 110/70. The general physical examination was negative, but the neurological examination revealed several positive findings.



Fig. 1.—A photograph of the fundus of the patient's right eye showing an area of chorioretinitis indicated by the arrow. The circular white areas are reflections of light.

The cranial nerves were normal except for II and VIII. Funduscopic examination of the eyes showed a bilateral papilledema of about two diopters. The retina of the right eye, as shown in Fig. 1, had a large central area of degeneration with patches of black pigment, white exposed sclera, and some choroidal vessels. The area was about two disc diameters across and was sharply demarcated. The left retina had two smaller areas of degeneration which consisted of black pigment deposits one-fourth disc diameter across. These areas were interpreted as evidence of chronic chorioretinitis. There was no indication that this was an active process. The visual fields for both eyes were normal peripherally, but there was a large central scotoma in the right field. The visual acuity was nearly zero in the right eye and 20/160 in the left. Audiogram readings revealed a slight loss of hearing in the right ear in the low frequencies; readings of the left ear were normal. The superficial and deep reflexes were normal throughout, except for hyperactivity of the knee and ankle jerks. The great toe signs were negative. A fine tremor, which was accentuated on exertion, was present in both hands but was more prominent in the left. While coordination was slightly impaired, sensation was intact throughout.

Laboratory examinations showed the urine, hemoglobin, white blood cell count, and differential, as well as the sedimentation rate, to be normal. The Mantoux and Wassermann tests were negative. Roentgenograms of the skull showed evidence, as seen in Fig. 2, of a generalized increase in intracranial pressure. One small area of calcification could be seen. This was thought to be in the choroid plexus. The possibility of the patient having toxoplasmosis was suspected because of the unexplained chorioretinitis and signs of chronic increased intracranial pressure. Neutralization tests* against toxoplasma carried out by one of us (C. E.) proved to be positive.



Fig. 2.—A roentgenogram of the patient's skull showing the scalping of the inner table due to increased intracranial pressure and also a small area of calcification indicated by the arrow.

A ventriculogram was performed on July 8, 1944, because it seemed urgent to relieve the increased intracranial pressure. This revealed the presence of a marked hydrocephalus of the lateral ventricles and the third ventricle but no filling of the aqueduct of Sylvius or of the fourth ventricle as seen in Fig. 3. Since there were no other findings in the neurological examination suggestive of a cerebellar or a midbrain tumor, the tentative conclusion was reached that the obstructing lesion was probably inflammatory in character and was due to the *Toxoplasma* infection. On July 12, 1944, the posterior fossa was exposed through a suboccipital incision and the arch of the first cervical vertebra was removed by Dr. W. T. Peyton, to whom we are indebted for a description of the surgical procedures employed. When the cisterna magna was opened, fluid appeared to come from the third ventricle through the aqueduct. Nevertheless, a Thorkildsen type of drainage

*An intracutaneous test done on the back of a rabbit using various dilutions of the toxoplasma with the patient's undiluted serum.

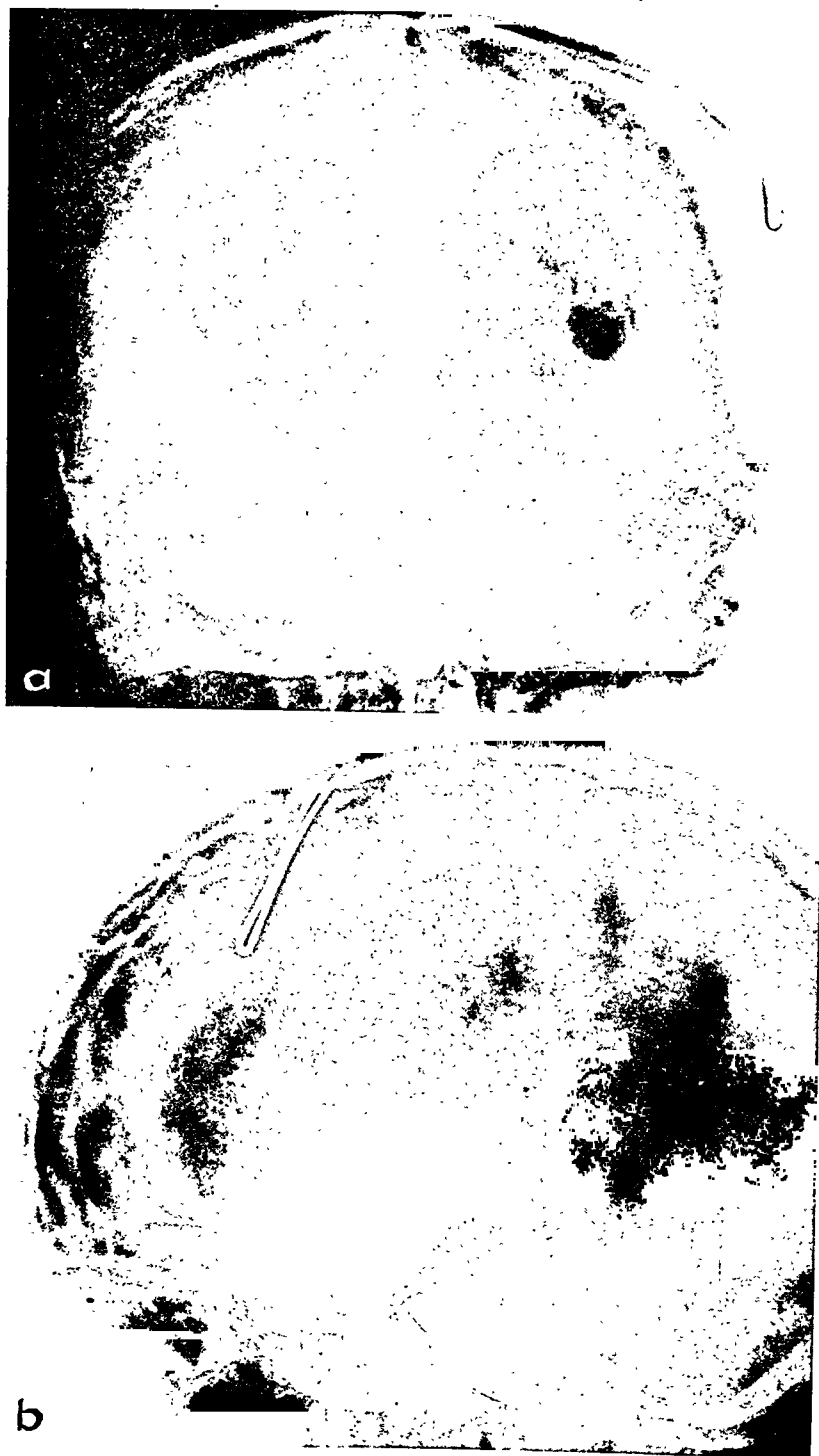


Fig. 3.—*a*, Anteroposterior and *b*, lateral views of the skull and brain as shown in a ventriculogram. Marked hydrocephalus of the lateral and third ventricles but no filling of the aqueduct or fourth ventricle can be made out.

of the right lateral ventricle into the cisterna magna was carried out, a properly fashioned lucite tube 3 mm. in diameter being used instead of a rubber catheter.

Subsequent to this operation the patient was symptomatically improved for a while but then became progressively worse. She complained of headache, became apathetic and incontinent, and the operative wound began to bulge. On August 14, 1944, the lucite tube was removed and the choroid plexus in the right lateral ventricle was destroyed by coagulation. It was felt that the *Toxoplasma* in some way might have caused a decrease in the absorption of cerebrospinal fluid, thereby upsetting the secretion-absorption balance. Such an imbalance has in some instances been corrected by destroying part of the choroid plexus.

Her immediate postoperative course was uneventful except for one generalized convulsion. Since the last operation the patient has shown progressive improvement with a complete cessation of headaches, vomiting, tinnitus, epistaxis, lethargy, and pain in the eye. She occasionally complains of scotomas, but this symptom is undoubtedly due to an irreversible process related to the chorioretinitis. There has been observed a gradual increase in visual acuity in the left eye. With correction of a fairly marked refractive error, the visual acuity in the left eye was found to be 20/20 in January, 1945. The vision in the right eye was not improved.

While psychometric tests were unfortunately not carried out before cauterization of the choroid plexus was done, six months following this procedure the patient showed an intelligence quotient of 109 on the Stanford-Binet scale. Such a high rating seemed quite remarkable in view of the severe hydrocephalus known to have been present.

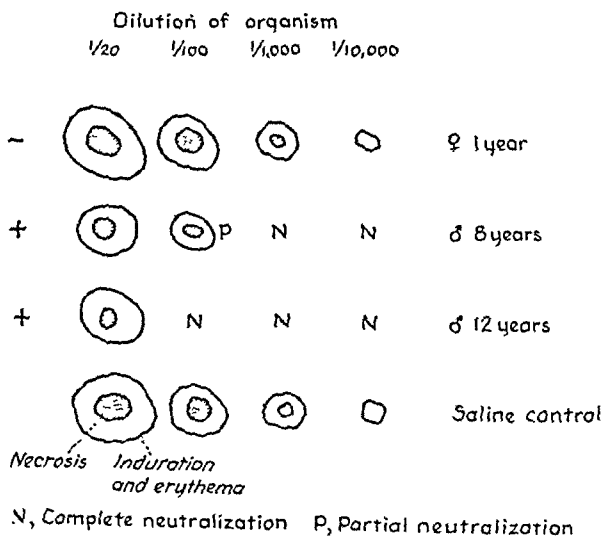


Fig. 4.—A freehand tracing of lesions from the intracutaneous neutralization tests done on the back of a rabbit. Three of the siblings, with varying degrees of neutralization, and a saline control are shown. The 1-year old sibling is the only one who showed no neutralization.

Since the clinical diagnosis of toxoplasmosis was confirmed by the positive neutralization test, blood for similar tests was obtained also from the mother, father, grandfather, two great aunts, and nine siblings of the patient. All of the siblings tested showed positive neutralization tests except the youngest child who was 12 months of age at the time. Several examples of the tests are shown in Fig. 4. The mother's neutralization was fully as strong as the patient's. The father and the two maternal great aunts of the patient were negative. However, the serum of the patient's maternal grandfather did show slight neutralization, the significance of which is problematical. These results are briefly summarized in Fig. 5.

Following the discovery of the many positive neutralization tests in this family against the *Toxoplasma*, we became interested in determining how many of the members exhibited the signs and symptoms of the disease. Accordingly each sibling and the mother of the patient were given a complete physical and neurological examination, including funduscopic study. Roentgenograms of the skull of each subject were obtained and the hemoglobin, white blood cell counts, and sedimentation rates were done on each. All of the siblings and the mother were found to be normal on these physical, laboratory, and x-ray examinations except for the presence of a corneal scar in one eye of the mother which had been present since she was 3 years of age.

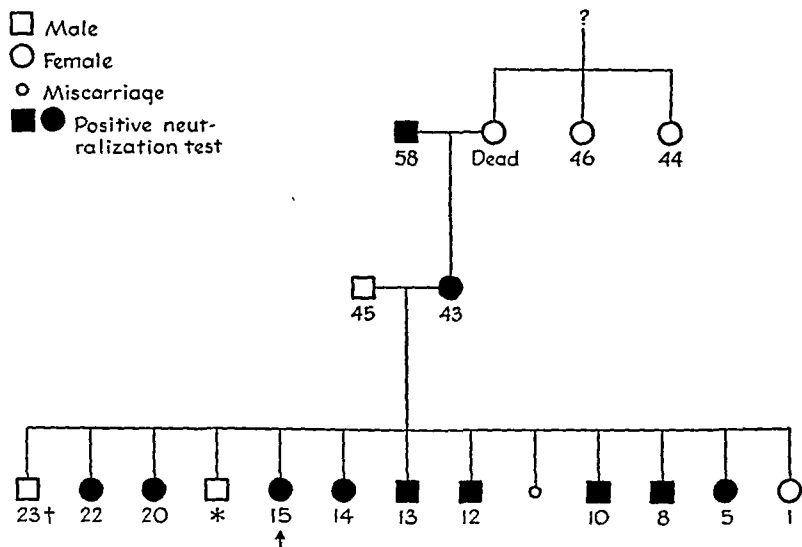


Fig. 5.—A pedigree chart showing the number of positive neutralization tests found in the family of C. G. The arrow points to the patient, C. G.

†Indicates a healthy sibling not tested.

*Indicates a full term infant who died of an enlarged head soon after birth.

DISCUSSION

Toxoplasmosis probably occurs in infants and children with much greater frequency than is at present appreciated. It should be considered in the differential diagnosis of all cases showing hydrocephalus, microcephaly, chorioretinitis, cerebral calcification, psychomotor disturbances, encephalitis, and atypical pneumonia accompanied by a spotted-fever-like rash. That the disease can be acquired in utero appears to have been demonstrated beyond question. The *Toxoplasma* probably crosses the placental barrier and infects the fetus. The infection can manifest itself at an early age, thereby producing a fetus or a newly born infant with hydrocephalus or microcephalus, or it can remain relatively latent until early childhood. Without serologic tests in early infancy or definite knowledge of the mother's infection having existed before the child's birth, it is impossible to determine with certainty whether the disease in an older child is congenital or acquired. Positive neutralization tests in the siblings as well as in the mother might merely mean that all had acquired the infection from a common source. The fact that the only sibling of our patient, C. G., to show a negative neutralization test was an infant might be interpreted as in-

dicating that infection in the others was acquired post partum, but this circumstance alone does not constitute adequate proof for such a conclusion. An intensive investigation of the farm animals and wild life of the region as a possible source for this infection is contemplated. The positive neutralization tests in the siblings of our patient who had no signs or symptoms of toxoplasmosis when examined merely indicates that they have been infected, whether ante partum or post partum.

The complete and prolonged relief of symptoms caused by progressive hydrocephalus in our patient by partial coagulation of the choroid plexus is a point of special interest. The fact that her intelligence had been little if at all impaired by the degree of hydrocephalus present is likewise worthy of special note. This, together with the recency of development of acute symptoms and signs of increased intracranial pressure, indicates that blockage of the ventricular system could not have been present over a long period of time.

SUMMARY

1. A typical case of toxoplasmosis occurring in a 14-year-old girl is reported.
2. Positive neutralization tests against the *Toxoplasma* organism were present in the patient, her mother, and eight of nine siblings tested.
3. The mother and the nine siblings had no clinical symptoms or signs of toxoplasmosis as determined by physical and roentgenologic examination.
4. Partial coagulation of the choroid plexus gave complete and prolonged relief of symptoms due to hydrocephalus.
5. Preservation of essentially normal intelligence in spite of the presence of fairly marked hydrocephalus was notable.
6. Whether infection in this patient and her siblings was congenital or acquired could not be ascertained from the available data.

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ADDENDUM

Since this manuscript was submitted, we have had an opportunity to examine and do serologic tests on the oldest sibling of our patient. Physical examination, including fundusoscopic and roentgenologic tests, was entirely normal on this sibling; however, several neutralization tests against the toxoplasma were definitely positive.

A COMPARATIVE STUDY OF THE "IMMUNE RESPONSE" TO VARIOUS PERTUSSIS ANTIGENS AND THE DISEASE

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THE primary objectives of this investigation were first, to learn what factors are involved in pertussis immunity; and, secondly, to determine what constitutes an effective prophylactic agent against pertussis.

Within the last few years the value of *Hemophilus pertussis* vaccines for active immunization against whooping cough has received considerable attention and has been the object of extensive clinical investigations. The results obtained by a number of workers, summarized by Maclean,¹ Strean and associates,² and the Council of Pharmacy and Chemistry of the American Medical Association,³ show that, although the immunity produced is substantial, it is not of the solid type known to occur after some other prophylactic, such as diphtheria toxoid. Likewise antibacterial serum for treatment and bacterial antigen for testing susceptibility have not yielded results sufficiently conclusive to warrant universal usage of these agents.

H. pertussis is known to elaborate a toxin which is lethal for mice, guinea pigs, and rabbits when injected intravenously, and dermonecrotic in small doses. In agreement with Evans⁴ and Strean⁵ it seems reasonable to believe that resistance to such a potent toxin which is also antigenic might have some importance in immunity.

In view of the importance of pertussis endotoxin and antiendotoxin (Strean⁶⁻¹⁰), it was deemed advisable to study the nature of this material as compared with pertussis bacterial vaccines and the Lederle Detoxified Antigen. The latter is prepared from the filtrate of pertussis broth cultures, whereas the pertussis endotoxin is prepared by physical disruption of the organisms, followed by subsequent chemical treatment. In this direction animal and clinical studies were conducted.

ANIMAL EXPERIMENT

Six rabbits which gave identical skin reactions to .025 M.L.D. and .037 M.L.D. of glycerinated toxin were chosen. Two rabbits were immunized with the detoxified pertussis antigen, two rabbits with Sauer's vaccine, and two rabbits were designated as control animals. The rabbits were injected subcutaneously, once each week, so that after six weeks each had received a total of 6 c.c. of the respective antigen. The first inoculation consisted of a 0.5 c.c. dose, the next four injections were of 1 c.c. amounts and the last inoculation was a 1.5 c.c. dose. The animals were tested for antitoxin and agglutinins two weeks after the final inoculation.

Antibody Titration Techniques.—The antitoxic response was titrated in minimum reactive doses (M.R.D.) determined by intradermal inoculations of

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We wish to acknowledge our gratitude to Ayerst, McKenna & Harrison, Limited, Rouses Point, N. Y. and to Lederle Laboratories, Inc., Pearl River, N. Y. for materials provided in the conduct of this study.

0.2 c.c. of toxin diluted in saline. The end point (M.R.D.) was the highest dilution that caused a necrotic area in the control rabbits. On this basis we determined the number of minimum reacting doses of toxin against which the immunized animals were protected.

The agglutination response was determined by a macroscopic tube agglutination test. Tubes 10 by 75 mm. were used. In the first tube 0.1 c.c. of serum was added to 0.4 c.c. of 0.85 per cent sodium chloride by means of a calibrated capillary pipette. After mixing twenty times by withdrawing into the pipette, 0.25 c.c. of the original dilution was transferred to the second tube to which 0.25 c.c. of 0.85 per cent of sodium chloride had been added. Subsequent dilutions were made similarly until 9 dilutions of serum had been made.

To the 0.25 c.c. of diluted serum in each tube, 0.25 c.c. of antigen (100 billion organisms of Phase I per cubic centimeter) was added. This gave final serum dilutions of 1:10 to 1:2,560. The tubes were shaken for two minutes and placed in the 37° C. incubator for two hours, with occasional shaking. The tubes were read with the naked eye by holding them against an ordinary bull's eye microscope lamp in a darkened room.

Procedure.—For the intradermal titration of the toxin, we removed the hair from the backs of the rabbits by means of a barium sulfide-starch depilatory mixture. We then marked the depilated areas into appropriate squares with carbol fuchsin. Inoculations of 0.2 c.c. amounts were made.

Results.—The highest dilution producing necrosis in the control rabbits was that of 1:160. Since there was necrosis at the 1:160 dilution and not at the 1:320 dilution, the critical dilution may have been somewhere between these two values. The necrosis at 1:160 did not appear very strong and, therefore, it did not seem likely that a much higher dilution would give necrosis. Nevertheless, dilutions ranging from 1:160 through 1:320 were made up so that dilutions of 1:160, 1:180, 1:200 were used for the final titration. Necrosis was again produced only at the 1:160 dilution, the 1:180 dilution showing only a slight suggestion of inflammation but no definite necrosis. Therefore, 0.2 c.c. of a 1:160 dilution represents the M.R.D. value of the toxin supplied to us by the Lederle Laboratories.

NECROTIC EFFECT OF PERTUSSIS TOXIN IN IMMUNIZED ANIMALS

CONTROL		SAUER		DETOXIFIED ANTIGEN	
				Undiluted Toxin*	
1:10*	1:320	1:50*	1:80*	1:2	1:16
1:20*	1:640	1:10*	1:160*	1:4	1:32
1:40*	1:960	1:20*	1:320	1:8	1:64
1:80*	1:1280	1:40*	1:640		
1:160*	Saline				

*Necrosis.

Since the rabbits immunized with Sauer's vaccine also showed necrosis in the 1:160 dilution we may conclude that these rabbits were unable to neutralize the toxin and had no antitoxic immunity.

The rabbits immunized with Lederle toxoid showed no necrosis up through the 1:2 dilution but did show necrosis with the undiluted toxin. These ani-

mals are therefore not resistant to 160 M.R.D. but are protected against 80 M.R.D. of toxin.

Thus, we have demonstrated that the Lederle detoxified antigen produces an antitoxic immunity not evoked by immunization with a bacterial vaccine like Sauer's.

Now let us consider the results obtained with the agglutination test previously described. The serum of the control animals produced agglutination through a titer of 1:40, but not 1:80. Of the two animals immunized with the detoxified antigen, one gave an agglutination of 1:160 and the other at 1:320. The animals immunized with Sauer's vaccine gave a strong agglutination at the highest dilution then made, 1:2,560. We therefore made further dilutions up to 1:25,000 and obtained agglutination at 1:15,000 for the serum of one animal. For the serum of the other animal an agglutination was produced at a titer of 1:10,000. These results are summarized in Table I.

TABLE I. AGGLUTINATION OF PHASE I ORGANISMS WITH THE SERUM OF THE IMMUNIZED AND CONTROL ANIMALS—EXPERIMENT 1

ANIMAL	FINAL SERUM DILUTIONS WITH PHASE I SUSPENSION													
	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	10	20	40	80	160	320	640	1,280	2,560	5,000	10,000	15,000	20,000	25,000
Detoxified antigen 1	+	+	+	+	+	0	0	0	0	—	—	—	—	—
Detoxified antigen 2	+	+	+	+	+	+	0	0	0	—	—	—	—	—
Sauer 1	+	+	+	+	+	+	+	+	+	+	+	+	0	0
Sauer 2	+	+	+	+	+	+	+	+	+	+	+	0	0	0
Control 1	+	+	+	0	0	0	0	0	0	—	—	—	—	—
Control 2	+	+	+	0	0	0	0	0	0	—	—	—	—	—

The results obtained with agglutination by the sera of the Lederle-immunized rabbits indicate the presence of agglutininogen in the Lederle toxoid. Apparently, lysis of some of the organisms occurs during the six day cultivation in broth so that bacterial antigens as well as the toxin, are present in the filtrate.

TABLE II. SUMMARY OF ANTIBODY TITRATIONS—EXPERIMENT 1

ANIMAL	VACCINE (DOSAGE: 6 C.C. OVER SIX-WEEK PERIOD)	AGGLUTINATION TITER	NO. OF M.R.D. PROTECTED AGAINST
1	Sauer	1:15,000	0
2	Sauer	1:10,000	0
3	Detoxified antigen	1:160	80
4	Detoxified antigen	1:320	80
5	Control	1:40	0
6	Control	1:40	0

It may be noted, from Table II, that Sauer's vaccine shows a marked ability to produce agglutinins in animals immunized with this antigen. It is conceivable that the production of agglutinins plays an important role in the prophylaxis against pertussis.

ANIMAL EXPERIMENT 2

In addition to clinical investigation with combined endotoxoid vaccine (Strean) the following animal experiment was tried. Four animals were selected on the basis of their intradermal reaction to 0.025 M.L.D. of the exo-

toxin (Lederle) and the endotoxin (Strean). One received injections of Sauer's vaccine, one was immunized with detoxified exotoxin (Lederle) another rabbit was given injections with combined pertussis endotoxoid vaccine (Strean), while the fourth was designated as a control. Each animal received a total of 9 c.c. of the respective antigen and was inoculated with 1 c.c. amounts each week for the first five weeks, followed by 2 c.c. injections spaced two weeks apart. They were tested for agglutination and antitoxic immunity two weeks after the last inoculation.

Procedure and Results.—In this experiment we did not titrate the antitoxic immunity quantitatively, but compared the dermonecrosis of the immunized rabbits with that of the control rabbit qualitatively. The dermonecrosis was produced by intradermal injections of various dilutions of the Lederle exotoxin, and the Strean endotoxin. Two solutions of purified endotoxin were used: (1) endotoxin freshly reconstituted with saline; (2) endotoxin previously reconstituted with a 50-50 mixture of glycerol and broth and stored at 10° C. for one month. The Lederle exotoxin was also stabilized with 50 per cent glycerol. All of the toxin dilutions were made with nutrient broth and injected in 0.2 c.c. amounts intracutaneously. The skin reactions were observed seventy-two hours after the injections were made.

The agglutination titer was determined by macroscopic tube agglutination. The results are given in Table III.

TABLE III

VACCINE	SERUM DILUTIONS WITH PHASE I SUSPENSION							
	1	1	1	1	1	1	1	1
	500	1,000	5,000	10,000	15,000	20,000	50,000	100,000
Detoxified antigen	+	0	0	0	0	0	0	0
Combined endotoxoid vaccine	+	+	+	+	+	+	+	0
Bacterial vaccine	+	+	+	+	+	+	+	0

The following observations were made with reference to the activity of the toxins and the antitoxic immunity produced:

1. The necrosis produced by the endotoxin was greater than the necrosis produced by the exotoxin per minimal lethal dose as observed from the results obtained in the control rabbit.

2. The exotoxoid-immunized animal was resistant to the dermonecrotic effects of the endotoxin while the endotoxoid-immunized animal was resistant to the dermonecrotic effects of the exotoxin.

3. The Sauer-immunized rabbit showed little or no protection against the necrotic activity of the exotoxin but was partially protected against the dermonecrosis of the endotoxin.

4. There was no apparent difference in the dermonecrotic activity of the freshly reconstituted endotoxin as compared with the stored endotoxin stabilized in a fifty-fifty mixture of glycerol and broth.

These results suggest that the endotoxin contains a factor which is dermonecrotic but not lethal for mice, in addition to a factor both lethal for mice and dermonecrotic. The latter factor, in all probability, is identical with or

similar to the exotoxin. Sauer's vaccine appears to have protected against the dermonecrotic activity of the nonlethal factor but not against the dermonecrosis produced by the exotoxin.

The agglutination titer of the rabbit immunized with combined endotoxoid-vaccine (Strean) corresponded with that of the Sauer-immunized animal. The detoxified antigen (Lederle) produced agglutinins in low titer. Obviously, then, the combined endotoxoid-vaccine is as good for the stimulation of bacterial antibodies as Sauer's vaccine, and, in addition, is capable of producing antitoxic immunity against the endotoxin and the exotoxin.



Fig. 1.—Positive reaction

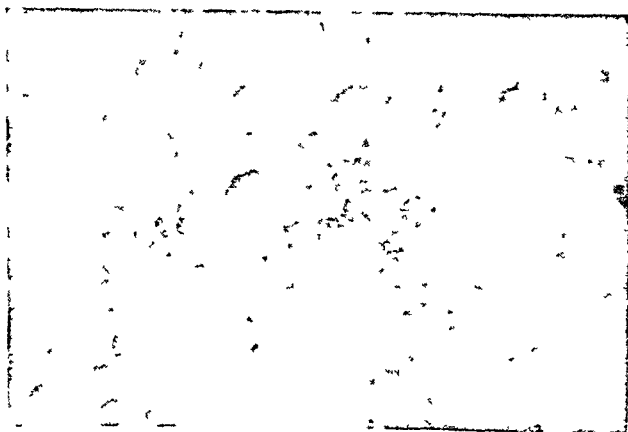


Fig. 2.—Positive reaction.

CLINICAL STUDIES

In order to study the immune response we performed antibody titrations on children at the Boston Health Department Well Baby Clinics, at the South Department of the Boston City Hospital, and at the Morgan Memorial Day Nursery. Thus, we were able to study the immune response in children who

had been inoculated with Sauer's vaccine, the Lederle antigen, and the Ayerst combined vaccine; in children during the course of illness and convalescence; and in children who had had the disease in years past. We utilized the agglutinin-opsonic index test for the detection of bacterial antibodies and the intradermal neutralization test in rabbits for the detection of circulating anti-toxin as well as the Strean skin test.

Antibody Titration Techniques.—The *agglutinin-opsonic index* was developed and used by us for the detection of circulating pertussis bacterial antibodies—the test is described herewith.

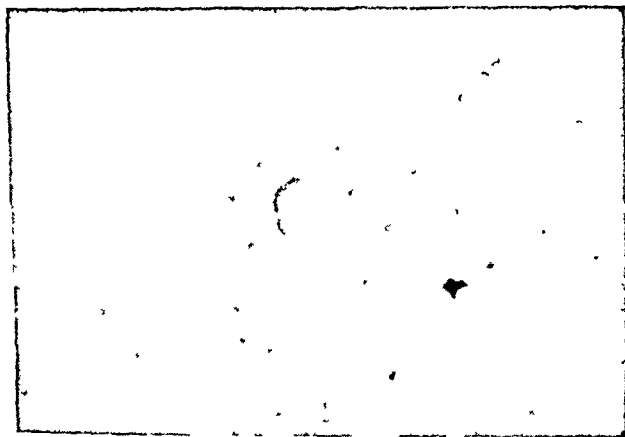


Fig. 3.—Positive reaction.

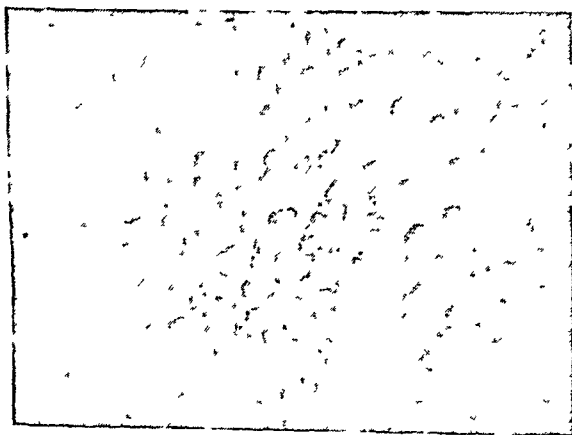


Fig. 4.—Negative reaction.

Antigen: A homogenous suspension in sodium citrate solution of killed pertussis bacilli (Phase I) standardized against positive and negative sera and adjusted to a turbidity of about 20,000 million organisms per cubic centimeter. The antigen is preserved in merthiolate 1:5,000.

Technique: The following technique was used: 0.1 c.c. of antigen is placed in a 3 by $\frac{3}{4}$ inch sterile tube. To this is added two drops (about 0.1 c.c.) of

whole blood. The blood and antigen are thoroughly mixed by rocking gently back and forth for one minute. The mixture is incubated at 37° C. for thirty to sixty minutes, with occasional shaking.

Preparation of Slides: The incubated mixture is rocked gently to redistribute the cells and organisms. With a capillary pipette, a drop of the blood-antigen mixture is placed on the end of a clean slide. The slide is placed on the table with the second index finger of one hand under the end which holds the drop. With a slide held in the other hand at an angle of about 30 degrees to the first, the drop is touched so that it follows this slide which is being drawn gently to the end of the first slide. By the time that the end of the slide is reached, the drop should be used up. The film is then dried in air and stained with Wright's stain in the usual manner.

A control is run consisting of 0.1 c.c. normal, negative blood with 0.1 c.c. of antigen.

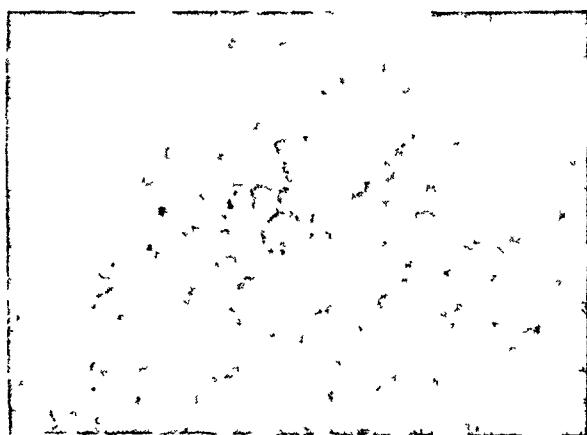


Fig. 5—Negative reaction

Examination of Slides: Examine under oil immersion, count twenty-five normal polymorphonuclear neutrophils and examine for phagocytosis. The opsonocytophagic activity is rated on a 4 plus basis.

- 1 plus: 15 to 20 of the 25 cells contain from 20 to 50 bacilli
- 2 plus: 20 to 25 cells contain from 20 to 50 bacilli
- 3 plus: At least 20 of the 25 cells contain 50 or more bacilli
- 4 plus: All 25 cells contain 50 or more bacilli

Agglutination: Observed on the same slide and rated on a 4 plus basis:

- 1 plus: Definite small clumps, scattered free bacilli
- 2 plus: Majority of organisms agglutinated, small clumps, few free bacilli
- 3 plus: Nearly all organisms agglutinated, large clumps and small clumps
- 4 plus: Complete agglutination, all large clumps

As a general rule, it is best to look for phagocytosis at the beginning of the smear and for agglutination toward the end of the smear.

THE TITRATION OF CIRCULATING ANTITOXIN

The titration of circulating antitoxin is based on a comparison of the necrosis produced by a standard toxin dilution with the necrosis produced by a serum-toxin mixture when injected intradermally in rabbits.

The total volume in the neutralization tube is 2.5 c.c. This volume contains 1 c.c. of serum plus toxin and broth. The contents of the tube are well mixed and placed in a 37° C. incubator for one hour. Two cubic centimeters of the dilution are then pipetted from the neutralized mixture into 2 c.c. of broth, in Wasserman tubes. The original dilution and the two successive 1:1 dilutions are injected into the test rabbits intradermally in 0.2 c.c. amounts (since rabbits vary in their sensitivity to the toxin it is necessary for the test rabbits to give a readable necrosis with 0.025 M.L.D. of toxin in order that they may be used for purposes of titration). Readings are made in from 48 to 72 hours. Each rabbit is also given a series of injections with control toxin dilutions. The controls are made so that one has a 0.025 M.L.D., a 0.037 M.L.D., a 0.05 M.L.D., and a 0.1 M.L.D. in a 0.2 c.c. injection of the dilutions of the standard toxin.

The antitoxin in the serum is estimated in units comparable to the M.L.D.'s of standard toxin neutralized by the serum. The amount of excess toxin present in a serum-toxin mixture is determined by a comparison of the necrosis produced with the toxin in the controls.

Antibody Titrations in Nursery Children.—A group of children enrolled in the Roof Nursery at several of the Boston Health Department Well Baby Clinics were tested for agglutination, opsonic activity, and circulating antitoxin. Several of the children had been previously immunized with Sauer's vaccine, a large number of them had had the disease, while others had neither been immunized nor ill with pertussis. Their histories with respect to pertussis were obtained from the files of the Well Baby Clinics. The results obtained are summarized in Table IV.

TABLE IV. RESULTS OF ANTIBODY TITRATIONS IN CHILDREN ENROLLED AT THE WELL BABY CLINICS OF THE BOSTON HEALTH DEPARTMENT

HISTORY	NO. OF CHILDREN	AGGLUTINATION					OPSONIC INDEX					ANTITOXIN	
		4+	3+	2+	1+	0	4+	3+	2+	1+	0	POSITIVE	NEGATIVE
Pertussis	24	1	3	6	3	11	3	5	11	1	4	3*	21
Sauer's	8	1	6	1				5	2	1		-	8
Negative	22			1		21	1	-	-	-	21	-	22

*Each of the three serum samples contained less than 0.3 unit of antitoxin.

THE AGGLUTININ-OPSONIC INDEX FOLLOWING PERTUSSIS INFECTION

In order to observe the production and persistence of circulating bacterial antibodies following a pertussis infection, fifty-one children from the West End and North End districts of Boston who had had pertussis in the past

TABLE V. THE AGGLUTININ-OPSONIC INDEX IN CHILDREN WITH A HISTORY OF PERTUSSIS

TIME ELAPSED SINCE CHILD HAD PERTUSSIS	NO. OF CHILDREN	AGGLUTINATION					OPSONIC INDEX				
		4+	3+	2+	1+	0	4+	3+	2+	1+	0
6 mo. to 1 yr.	10	-	2	5	3	-	-	6	2	2	-
1 to 2 years	16	1	-	5	9	1	1	3	6	6	-
2 to 3 years	18	-	1	2	12	3	-	7	6	3	2
Over 3 years	7	1	-	2	2	2	-	2	1	3	1
Total	51	2	3	14	26	6	1	18	15	14	3

few years were tested. The children varied in age from 18 months to 8 years. The results are summarized in Table V.

Agglutinin-Opsonic Index During Course of Illness.—In order to determine how soon pertussis antibodies were formed, we tested thirteen pertussis patients at the South Department of the Boston City Hospital by means of the agglutinin-opsonic index test. In addition, we also took nasopharyngeal cultures to demonstrate the presence of Phase I pertussis organisms. The results obtained are shown in Table VI.

TABLE VI. THE AGGLUTININ-OPSONIC INDEX IN PERTUSSIS PATIENTS AT THE SOUTH DEPARTMENT OF THE BOSTON CITY HOSPITAL

NAME	SEX	AGGLUTINATION	OPSONIC INDEX	NASOPHARYNGEAL CULTURE
R. P.	F	++	+	+
J. P.	M	+++	+++	-
S. P.	M	+++	++++	-
D. D.	M	++	+	-
K. B.	F	+	-	-
R. H.	F	+	++	+
H. B.	F	+	++++	-
B. S.	F	-	-	-
M. M.	M	+	-	+
R. E.	M	+	-	-
R. C.	M	++	+++	-
T. Mc.	M	+++	+++	-
M. H.	F	+	+	-

Interpretation of Results.—From the results summarized in Tables IV to VI we may conclude that the predominating "immune response" to a pertussis infection is the production of bacterial antibodies such as agglutinins and opsonins. The production of these antibodies begins early in the spasmodic stage of the disease, increases during the convalescent stage, and persists at a high level for at least several months to a year afterward. These antibodies are present in decreasing titers for several years after recovery from the disease in a comparatively large per cent of cases. Apparently there is some evidence of antitoxin production following recovery from the disease. However, the amount of circulating antitoxin that may be detected is rather minimal and was present in only a very few of the children studied. It must be admitted, nevertheless, that the limit of sensitivity of the test for circulating antitoxin does not permit the detection of much less than 0.3 of a unit of antitoxin.

Immunization with a bacterial vaccine such as Sauer's results in the production of agglutinins and opsonin in high titer. There is no evidence of the

production of antitoxin to a bacterial vaccine. These results are in essential agreement with the results of our animal experiments.

Antitoxin Titrations in Lederle-Inoculated Children.—Twelve children who had been inoculated with pertussis antigen (detoxified) were gathered at the West End Health Unit for antitoxin titrations. Most of the children were about 1 year old and had been inoculated between the ages of 6 and 9 months. The results are shown in Table VII.

TABLE VII. ANTITOXIC RESPONSE IN CHILDREN INOCULATED WITH PERTUSSIS ANTIGEN (DETOXIFIED)

SUBJECT	TIME SINCE INOCULATION	UNITS OF ANTITOXIN PER C.C. OF SERUM
1	3 mo.	0.3
2	11 mo.	0.0
3	6 wk.	1.2
4	6 wk.	0.5
5	10 mo.	0.0
6	1 yr. 1 mo.	0.0
7	5 mo.	0.8
8	1 yr. 3 mo.	0.0
9	3 mo.	0.4
10	7 mo.	0.0
11	4 mo.	0.3
12	4 mo.	0.3

These results indicate that antitoxin production follows immunization with a pertussis toxoid. However, the antitoxin levels are not high and when more than six months had elapsed since the last inoculation, no circulating antitoxin could be detected. The titers in human sera are considerably lower than those we obtained in rabbits. The rate of antitoxin production and the decline in the antitoxin level, however, appear to be similar. The maximum antitoxin level was reached at about six weeks after immunization and declined rapidly thereafter.

The Agglutinin-Opsonic Index and the Streak Test in Children at the Morgan Memorial Nursery.—Thirty-seven children, varying from 2½ to 4 years of age, were tested by the agglutinin-opsonic index method on one day and the Streak skin test on the following day. Four children who were not permitted to attend the nursery because of a suspicious cough were brought in and skin tested with the rest of the group. We also obtained cough plates from them. The results of the skin-testing were read after twenty-four hours and, as a check, we repeated our readings a second time. We found that our second set of observations was identical with the first. The results are shown in Table VIII.

A comparison of the results obtained with the Streak Test and the agglutinin-opsonic index showed that in 80 per cent of the subjects, there was essential agreement between the two tests. It was interesting to note that, even though bacterial antibodies were present, the Skin Test was strongly positive in five instances and doubtfully positive in two others. These conflicting results were present for the most part in children who had had the disease. This would seem to indicate that the antiendotoxic titer had dropped

TABLE VIII. THE AGGLUTININ-OPSONIC INDEX AND THE STREAN TEST IN CHILDREN AT THE MORGAN MEMORIAL DAY NURSERY

NAME	SEX	AGGLUTINATION	OPSONIC INDEX	SKIN TEST	HISTORY
E. D.	M	-	-	2+	Negative
E. W.	F	-	-	absent	Negative
S. E.	F	1+	1+	-	W. C. in 1942
G. G.	M	2+	1+	absent	W. C. in 1941
K. O.	F	-	-	1+	Negative
J. C.	M	-	-	2+	Negative
L. N.	F	-	-	3+	Negative
W. B.	M	-	-	2+	Negative
A. S.	F	1+	2+	-	Sauer's, 1941
N. C.	F	3+	2+	1+	Sauer's, 1942
W. R.	M	-	-	2+	Negative
J. F.	M	1+	2+	-	W. C. in 1940
R. V.	M	-	-	1+	Negative
A. S.	M	-	2+	-	W. C. in 1941
S. B.	M	2+	1+	-	W. C. in 1942
E. L.	F	2+	2+	absent	W. C. in 1942
G. D.	M	-	-	absent	Lederle toxoid, 1942
A. Z.	F	1+	2+	2+	W. C. in 1941
A. K.	F	1+	1+	-	W. C. in 1941
V. M.	F	1+	2+	-	W. C. in 1941
D. N.	M	-	-	1+	Negative
J. N.	F	1+	2+	1+	W. C. in 1942
M. D.	F	-	-	3+	Negative
L. B.	F	1+	1+	-	Lederle toxoid, 1942
R. B.	M	2+	2+	2+	Sauer's, 1942
C. T.	M	-	-	2+	Negative
A. H.	M	-	-	2+	Negative
B. S.	F	1+	2+	-	Negative
G. N.	F	-	-	2+	W. C. in 1941
L. E.	F	1+	2+	3+	W. C. in 1941
R. S.	F	-	-	2+	Negative
M. O.	F	1+	3+	-	Negative
B. O.	F	-	-	3+	Negative

SUPPLEMENTARY:

CHILDREN	SEX	SKIN TEST	COUGH PLATE
P. G.	M	-	Negative
E. K.	M	3+	Positive
A. C.	M	-	Negative
K. T.	M	1+	Positive

or that possibly the positive skin test was allergic and caused by the small amounts of agglutinin present in the skin-testing material. It has been impossible, to date, to prepare purified endotoxin entirely free from agglutinin. In persons who did not have a history of pertussis the Streaan Test gave us reliable results.

As for the four children who had suspicious coughs, two gave a positive skin reaction and two were negative. The fact that the two children with the positive Streaan test also gave rise to a positive cough plate and soon after developed clinical whooping cough may be regarded as significant.

Clinical Evaluation of the Streaan Test.—In order to further evaluate the Streaan test, a group of children whose histories were accurately recorded at the Well Baby Clinics of the Boston Health Department were skin-tested. The group included children who had been "immunized" with the Sauer vaccine, the Lederle antigen; children who had had pertussis; and some control chil-

TABLE IX. SUMMARY OF REACTIONS OBTAINED WITH THE STREAN TEST AT THE WELL BABY CLINICS OF THE BOSTON HEALTH DEPARTMENT

HISTORY	REACTIONS					
	NO. OF CHILDREN	DOUBTFUL	1 PLUS	2 PLUS	3 PLUS	NEGATIVE
Sauer	25	1	7	10	5	2
Lederle	26	1	12	8	1	4
Pertussis	21	1	0	2	1	17
Negative	26	1	10	7	1	7

TABLE X. PERCENTAGE OF POSITIVE, NEGATIVE, AND DOUBTFUL REACTIONS OBTAINED WITH THE STREAN TEST AT THE WELL BABY CLINICS OF THE BOSTON HEALTH DEPARTMENT

HISTORY	NO. OF CHILDREN	DOUBTFUL (%)	POSITIVE (%)	NEGATIVE (%)
Sauer	25	4.0	88.0	8.0
Lederle	26	3.8	80.8	15.4
Pertussis	21	4.8	14.3	80.9
Negative	26	4.5	81.9	13.6

dren who had never had pertussis or been immunized against the disease. A summary of the results appears in Tables IX and X.

It is significant to note that 80.9 per cent of children with a history of pertussis reacted negatively to the Streaan Skin Test while those immunized with Detoxified Antigen or Sauer's vaccine as well as the negative controls, reacted in the main positively. On the whole, there was good correlation between the Streaan Skin Test and the clinical histories of the children studied.

We also skin tested four infants who were about 2 months old. They were negative. Kunstler¹¹ reported the presence of neutralizing antibodies against pertussis endotoxin in newborn infants, which may explain these results.

The fact that we obtained positive skin tests in the majority of children who had been inoculated with the Lederle "Detoxified Antigen" does not agree with the results obtained in our experiments with rabbits. Rabbits immunized with the Lederle antigen were capable of neutralizing the dermo-necrotic effect of pertussis endotoxin. It would seem, therefore, that the positive skin test in these children was of an allergic type.

In order to observe the Streaan test in children inoculated with the Ayerst "Combined Pertussis Vaccine with Pertussis Endotoxoid" as an immunizing agent, as well as to ascertain whether or not the skin-testing material could elicit an allergic reaction, we performed the skin test using a heated toxin control as well as freshly reconstituted toxin. We used as subjects some of the children at the Morgan Memorial Nursery who had been inoculated with the "Combined Antigen." In addition we performed the agglutinin-opsonic index test on them. These children had received their last inoculation of the antigen two months earlier. The results of the tests are shown in Table XI.

Both the heated toxin control and the fresh toxin produced a sizable wheal on these children, indicating an allergic response. Obviously, then, unless the Streaan test is carried out with a heated toxin control, it may result in erroneous interpretations because of previous inoculations with a pertussis antigen or individual idiosyncrasies.

TABLE XI. THE AGGLUTININ-OPSONIC INDEX AND THE STREAN TEST IN CHILDREN IMMUNIZED WITH THE AYERST "COMBINED VACCINE"

NAME	SEX	AGGLUTINATION	OPSONIC INDEX	STREAN TEST	
				CONTROL	TEST
G. B.	M	3 plus	2 plus	3 plus	3 plus
W. B.	M	4 plus	3 plus	3 plus	3 plus
P. C.	M	3 plus	3 plus	2 plus	3 plus
D. K.	M	3 plus	2 plus	3 plus	4 plus
D. K.	M	3 plus	4 plus	2 plus	3 plus
G. N.	F	2 plus	2 plus	2 plus	2 plus
L. N.	F	3 plus	3 plus	2 plus	3 plus
R. V.	M	4 plus	3 plus	3 plus	3 plus
E. W.	F	3 plus	3 plus	3 plus	4 plus

The fact that good agglutination and opsonocytophagic activity were observed by the agglutinin-opsonic index test is good evidence for the antigenic quality of the immunizing agent.

SUMMARY

To study the immune response in animals and in human beings the following tests were used: agglutination reactions, the opsonocytophagic reaction, antitoxin titrations, and intradermal tests. A study of these reactions in immunized rabbits and in human beings, as well as in human beings during the course of illness and after recovery from the disease, was made. The results obtained indicate:

1. Sauer's vaccine gives rise to a substantial agglutination titer and opsonic index as well as to a small amount of antibody to a dermonecrotic endobacterial antigen.

2. Detoxified antigen produces antitoxin in moderate titer and agglutinins in low titer.

3. The combined bacterial vaccine and endotoxoid produces both antitoxin and bacterial antibodies in high titer.

4. The disease itself gives rise to a moderate agglutination titer, a good opsonin titer and antitoxin of exceedingly low titer. A tissue immunity to a toxic bacterial extract is developed.

5. The bacterial antibodies are produced rapidly and attain a maximum about two to three months after immunization. They appear in the circulation during the spasmodic stage of the disease and persist in high titer from six months to a year. These antibodies have been demonstrated from two to three years after recovery from the disease in a large per cent of the children studied.

6. The antitoxin level reaches a maximum about two months after immunization with the toxoid and falls rapidly thereafter. In six to seven months, little or no circulating antitoxin may be detected. Very little antitoxin, if at all, can be demonstrated in the blood of individuals who have recovered from the disease.

In assessing the value of the Strean skin test, it was found that 85 per cent of persons with a history of pertussis gave a negative reaction. On the other hand, about 90 per cent of the children immunized with Sauer's vaccine or detoxified antigen, as well as those with no history of pertussis or pertussis immunization gave a positive reaction. There is an indication that the positive results in the Lederle-inoculated group are due to an allergic reaction, that in the Sauer-immunized group it is both toxic and allergic, whereas in the group with a negative history of pertussis or immunization, the positive reaction is largely toxic. Apparently the material used was not free from agglutinin which gives rise to this allergic-type reaction. The Strean test indicates, in part, that the immune response after an attack of the disease is a highly efficient one. The Strean test is of definite value in determining susceptibility to pertussis when performed with a heated control.

An evaluation of the agglutinin-opsonic index test shows a high correlation between the opsonocytophagic activity and a history of pertussis. Agglutinins were not always detected together with the opsonins in children who had recovered from the disease but, in a majority of these children, both bacterial antibodies could be detected by the microscopic test. In immunized children the degree of opsonic activity paralleled the agglutinin activity. In children recovered from the disease the opsonic activity was invariably stronger than the agglutination reaction.

The results of a field investigation (pending publication in the *Journal of the American Medical Association*) indicate that Sauer-immunized children were afforded protection to a greater or lesser degree for about two years, the duration of this study. Immunization with pertussis detoxified antigen did not appear to offer any protection against an attack of pertussis but did modify the disease so that it was clinically milder in a majority of cases.

Immunization against pertussis toxin alone is not of value in prophylactic treatment of the disease, since agglutinative and opsonocytophagic antibodies are essential to protect against the initial invasion of the organism. Because some of the clinical manifestations are attributed to the action of pertussis toxin, it would be advisable to produce an immunity against this toxic factor. The "immune response" to a combined Phase I bacterial vaccine with pertussis endotoxoid more nearly corresponds to the immunity produced by an attack of pertussis.

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ONE DOSE SUBCUTANEOUS SODIUM SULFADIAZINE FOR ACUTE INFECTIONS

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THE subcutaneous administration of sodium sulfadiazine has become a more and more popular method in hospitals because of its simplicity and effectiveness. As used and studied at The Children's Memorial Hospital in Chicago,¹ this method can also be used in the care of a patient in his home, thus sparing the child hospitalization. The "one dose" oral or intravenous method has been described by several authors²⁻⁶ and we are about to discuss the "one dose" subcutaneous method.

This method should permit the physician to treat at home the patient who is in need of intensive sulfonamide therapy but unable to take or retain oral medication. The subcutaneous route will avoid the rather difficult intravenous administration in small children and, furthermore, the single dose may "decrease the risk of toxic manifestations, the sensitization to the drug and the cost of treatment."²

We have treated twenty-four patients with acute upper and lower respiratory infections by giving them approximately 1 grain per pound of body weight of a 5 per cent solution of sodium sulfadiazine in distilled water subcutaneously. The solution was injected by syringe in one thigh, or, if necessary, divided in two portions and given in both thighs (Table I).

There was no untoward local reaction in any of our cases. Of the twenty-four patients in our series, ten had definite symptoms and signs of pneumonia, and the diagnosis was verified by x-ray pictures. Eleven had rather severe pharyngitis, tonsillitis, or otitis, or a combination of those infections. Of these twenty-four patients, nineteen received the one injection as their only sulfonamide treatment during their entire illness and they recovered rapidly. The response of the temperature curve and the drop in the leucocyte count was very dramatic in almost all cases. Subjectively and objectively these patients recovered very speedily. That frequent medications and repeated injections were not necessary was appreciated by the patient as well as the nursing staff.

In five cases the sulfonamide therapy was continued orally or subcutaneously for various reasons.

Case 1.—In this case of a child with pneumonia the temperature rose on the third day after the initial dose and remained elevated. On the seventh day it was felt to be advisable to start oral sulfonamide therapy. The patient recovered uneventfully. This was our first patient in this series and the delay in oral therapy may have prolonged the hospitalization. In our later cases we felt that in the event of a secondary temperature elevation or in very severe infections sulfonamide should be restarted and administered for a prolonged time.

From The Children's Memorial Hospital.

CASE	AGE	WEIGHT (POUNDS)	SULFA- DIAZINE (GRAINS)	SODIUM BIOCAR- BONATE	TEMPER- ATURE RESPONSE WITHIN	TREATMENT SUCCESS	DIAGNOSIS
1. C. T.	4½ yr.	31	37.5	+	24 hours Secondary rise in 3 days	Oral sulfon- amide re- started	L.L.L.; pneumonia
2. M. B.	2½ yr.	25½	30.0	+	24 hours	Recovered	L.U.L.; pneumonia
3. F. H.	2½ yr.	25	30.0	+	24 hours Secondary rise in 2 days	Oral sulfon- amide restarted	Left empyema
4. K. K.	6 yr.	40½	45.0	+	24 hours	Recovered	Pharyngitis; tonsillitis
5. R. M.	2½ yr.	32	37.5	-	24 hours	Recovered	Nasopharyn- gitis
6. J. B.	4 yr.	30	37.5	-	24 hours	Recovered	Pharyngitis; tonsillitis; pneumonia
7. G. J.	3 yr.	28	37.5	+	24 hours	Recovered	Left broncho- pneumonia
8. J. D.	3½ yr.	31½	37.5	+	24 hours	Recovered	L.U.L.; broncho- pneumonia
9. D. F.	1½ yr.	26	18	+	24 hours	Recovered	Pharyngitis; otitis media
10. A. D.	1½ yr.	21	25	+	No tempera- ture	Recovered	Nasopharyn- gitis
11. P. D.	2 yr.	21	30	-	48 hours	Recovered	Roseola in- fantum
12. G. K.	1½ yr.	28	30	-	24 hours	Recovered	Pharyngitis; otitis
13. G. S.	1 yr.	23	30	+	24 hours	Recovered	Bronchopneu- monia
14. D. C.	3½ yr.	27	33	+	24 hours	Recovered	Bronchopneu- monia; L.L.L.
15. R. K.	6 yr.	52	45	-	24 hours	Recovered	Tonsillitis; otitis
16. C. S.	2 yr.	20	20	+	24 hours	Recovered	Pharyngitis; bronchitis
17. M. M.	6 yr.	45	45	+	24 hours	Oral sulfon- amide restarted	Otitis media; mastoiditis
18. T. T.	10 yr.	79	45	-	24 hours	Oral sulfon- amide restarted	Ruptured appendix
19. B. P.	3 yr.	34½	37.5	+	24 hours	Recovered	Pharyngitis; cervical adenitis
20. M. D.	5 yr.	37½	45	+	24 hours	Recovered	Follicular ton- sillitis
21. J. H.	6 yr.	43	45	-	24 hours	Recovered	Otitis media; tonsillitis
22. D. M.	4 mo.	15½	15	+	24 hours	Recovered	Pharyngitis; otitis; bronchopneu- monia
23. W. N.	6 mo.	12½	15	-	24 hours	Recovered	U.R.I.; bronchitis
24. L. M.	8 yr.	42½	45	+	48 hours	Oral sulfon- amide restarted	R.U.L.; pneumonia

L. L. L., left lower lobe; L. U. L., left upper lobe; U. R. I., upper respiratory infection;
R. U. L., right upper lobe.

X-RAY DIAGNOSIS	WHITE BLOOD COUNT		URINALYSIS SULFADIAZINE CRYSTALS			PRES- ENCE OF BLOOD	BLOOD CONCENTRATION			
							(HR.)		(MG.)	
	DAY	LEUCOCYTES	DAY	+	-	+	-	(HR.)	(MG.)	(HR.)
Confirmed	1	33,200	1	-	-	-	-	1	26.8	9
	2	26,700	2	+	-	-	-	2	32.9	19
	3	14,250	3	-	-	-	-	3	33.8	30
	5	16,900						4	31.5	
Confirmed	1	21,800	2	-	-	-	-	1	28.4	6
	2	18,550	3	-	-	-	-	2	33.8	17
	3	9,300	4	-	-	-	-	3	37.4	23½
								4	36.2	28½
Confirmed	1	11,400	1	-	-	-	-	1	21.1	17½
	2	13,850	2	-	-	-	-	2	21.8	22
	3	10,500						3	28.2	26
								4	26.0	
None taken	2	9,200	2	-	-	-	-	None taken		
			3	-	-	-	-			
None taken	1	35,300	1	-	-	-	-	None taken		
	2	18,200	2	-	-	+	-			
Confirmed	2	23,800	2	+	-	-	-	13	17.0	
			26	-	-	-	-	18	14.0	
Confirmed	1	33,000	3	-	-	-	-	None taken		
	2	21,700	5	-	-	-	-			
Confirmed	1	32,650	1	-	-	-	-	None taken		
			2	-	-	-	-			
Lungs clear	4	8,100	3	-	-	-	-	None taken		
Lungs clear	4	6,650	2	-	-	-	-	None taken		
None taken	2	4,850	2	+	-	-	-	None taken		
	6	4,900								
Lungs clear	2	4,000		None taken				None taken		
None taken	2	6,070	3	-	-	-	-	None taken		
Confirmed	2	7,700	2	-	-	-	-	None taken		
			9	-	-	-	-			
Lungs clear	2	5,350		None taken				1	16.0	21
								2	16.6	
								3	14.3	
								4	13.0	
None taken	2	20,850	2	-	-	-	-	None taken		
None taken	2	15,500	2	+	-	-	-	12	17.0	
			14	-	-	-	-			
None taken	2	21,950	2	+	-	-	-	15	8.0	
	4	11,670								
None taken	3	10,600	2	+	-	-	-	10	19.8	
			3	-	-	-	-			
			17	-	-	-	-			
Clear lungs	2	20,500	1	-	-	-	-	1	23.6	21
			2	+	+	-	-	2	25.7	
			4	-	-	-	-	3	25.7	
Bronchitis	2	18,600	1	-	-	-	-	13½	12.8	
			2	-	-	-	-			
			18	-	-	-	-			
None taken	10	6,100	1	+	+	-	-	None taken		
			2	+	-	-	-			
			9	-	-	-	-			
None taken	2	10,450	2	-	-	-	-	2	27.0	
Confirmed	3	11,150	1	-	-	-	-	None taken		
			2	-	-	-	-			

Cases 3, 17, 18, 24.—The severity of the symptoms in these cases induced us to continue sulfonamide therapy twenty-four hours after the initial dose was given. The cases represented an empyema, a mastoiditis, a ruptured appendix, and a case of very poor general condition.

Sulfadiazine blood level determinations showed that a very satisfactory concentration was reached in less than one hour after administration and that it remained within a therapeutic range for from twenty-four to thirty-six hours.

In sixteen cases sodium bicarbonate was given, either starting simultaneously with the sulfonamide or somewhat later. The urine was examined in all but two cases and sulfadiazine crystals were reported in eight cases. Of these eight patients, five received sodium bicarbonate and three did not. The urine showed red blood cells in three cases and of those two patients received sodium bicarbonate. The small number of cases does not permit any conclusion as to the relationship of alkalinization and urinary findings. However it proves that, as tested by repeated urinalyses, in our series no serious or lasting damage to the kidneys occurred. It may be mentioned at this point that two of our patients received parenteral fluids and that alkalinization, if desired, can be obtained by subcutaneous fluid administration.

SUMMARY AND CONCLUSION

A method of treatment of acute infections by a single subcutaneous administration of sodium sulfadiazine has been studied on twenty-four patients and is tabulated.

We believe that this method of treatment may be of use to the practicing physician in treating his patients in their homes. It may also be used to advantage in the ambulatory clinic patient and in rural communities where hospitalization facilities are scarce. No trained personnel is needed and the nursing care of the patient is simplified.

This method is not recommended in cases of pneumonia with complications or for very severely ill patients who should receive a regular course of sulfonamide therapy following the initial injection.

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COMPARISON OF ABSORPTION OF VITAMIN A AFTER ORAL AND INTRAMUSCULAR ADMINISTRATION IN NORMAL CHILDREN

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THE parenteral administration of vitamin A has been widely recommended and used, especially for patients having pancreatic cystic fibrosis.

After the work of Andersen^{1, 2} and other authors, the pulmonary changes associated with pancreatic achylia have been related to vitamin A deficiency, because squamous metaplasia of the epithelium has been found, but whether the lack of the vitamin is the only cause of the pathologic lesions is still unknown. At any rate, the pulmonary condition often does not improve despite the administration of large amounts of the vitamin given over long periods of time. This negative result, obtained by all the people who have worked with fibrocystic disease of the pancreas, was brought to my attention by experience at Bobs Roberts Hospital in Chicago in treating a patient who received 50,000 I. U. intramuscularly daily during fifteen days and subsequently every third day for six months. Periodical chest x-ray films never showed any improvement whatsoever.

May and others⁴ have demonstrated that vitamin A when administered orally is not absorbed well by these patients. Experience led us to believe that parenterally administered vitamin was also not absorbed. This was confirmed in our patient by an absorption curve made following intramuscular injection of 10,000 I. U. of vitamin A per kilogram of body weight, which showed no rise whatever in the serum levels of vitamin A. No control data regarding absorption curves following parenteral administration of vitamin A in normal children have been found in the literature. A study of the absorption of vitamin A after intramuscular injection in children without abnormalities in digestion or fat metabolism was therefore undertaken.

Injectable vitamin A (1 c.c. = 50,000 I. U. in sesame oil)* was given in doses of 10,000 I. U. per kilogram of body weight. The same source of vitamin was used for both oral and parenteral tests. The material was injected into the muscles of the buttocks. Blood was obtained at the moment of the administration and three, six, nine, and twenty-four hours after parenteral injection, and after three and six hours when the vitamin was given orally. In some patients receiving the vitamin orally, only fasting and 6-hour specimens of blood were taken, since our chief object was to determine whether these patients had a normal absorption of vitamin A. The determination of the vitamin was made according to the method described by May, and associates.⁴

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*The vitamin preparation used in this study was made by Endo Products, Inc., Richmond Hill, N. Y.

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TABLE I. SERUM VITAMIN A AFTER ORAL ADMINISTRATION

NO.	DIAGNOSIS	AGE (YR.)	FASTING		3 HR. LATER		6 HR. LATER	
			CAROTENE $\gamma/100$ C.C.	VITAMIN A I.U./100 C.C.	CAROTENE $\gamma/100$ C.C.	VITAMIN A I.U./100 C.C.	CAROTENE $\gamma/100$ C.C.	VITAMIN A I.U./100 C.C.
1	Rheumatic fever	8	10.5	122			9.0	576
2	Ménière's syndrome	9	9.6	148			9.0	770
3	Poliomyelitis convalescent	7	15.3	155			16.0	614
4	Rheumatic fever	9	4.4	160			3.7	715
5	Rheumatic fever	6	10.2	154			9.8	549
6	Cerebral tumor	9	8.2	140	7.8	310	7.8	840
7	Upper respiratory infection	2	25.2	154	25.4	286	28.2	920

TABLE II. SERUM VITAMIN A AFTER INTRAMUSCULAR INJECTION

NO.	FASTING		3 HR. LATER		6 HR. LATER		9 HR. LATER		24 HR. LATER	
	CAROTENE $\gamma/100$ C.C.	VITAMIN A I.U./100 C.C.	CAROTENE $\gamma/100$ C.C.	VITAMIN A I.U./100 C.C.	CAROTENE $\gamma/100$ C.C.	VITAMIN A I.U./100 C.C.	CAROTENE $\gamma/100$ C.C.	VITAMIN A I.U./100 C.C.	CAROTENE $\gamma/100$ C.C.	VITAMIN A I.U./100 C.C.
1	9.0	139	9.0	139	10.6	154	10.0	156	10.6	140
2	8.8	142	8.6	140	8.8	142	8.6	148	8.8	180
3	15.6	155	16.2	152	15.8	156	15.2	152	15.8	184
4	4.6	158	4.4	150	4.2	146	4.8		4.8	152
5	12.4	101	12.2	99	12.6	91	12.2	98		
6	7.8	180	8.0	192	8.6	178	7.8	178		
7	25.0	135	25.4	198	25.8	153	25.8	158		

As shown in Table I, all the patients who received vitamin A by the oral route experienced a marked rise in vitamin level after six hours when, according to May and associates,⁴ the vitamin A concentration is at its highest level in the plasma. Table II shows that the vitamin was not utilized at all when given parenterally. In some patients the serum vitamin A concentration was assayed twenty-four hours after parenteral administration. This experiment was based on comparable tests performed in dogs by Clausen,³ who found that when vitamin A was given intramuscularly, the highest level was obtained after twelve or twenty-four hours. In all our patients from whom we took blood after twenty-four hours, the vitamin concentration was approximately the same as at the beginning.

It is concluded that the parenteral administration of vitamin A fails to raise its concentration in the circulating blood.

SUMMARY

A comparison has been made between vitamin A absorption curves following oral and parenteral administration of the vitamin in seven children without digestive symptoms. In all cases the oral administration resulted in normal absorption, while the parenteral administration showed little or no evidence of absorption.

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LACUNAR SKULL OF THE NEWBORN INFANT

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LACUNAR skull is an anomaly of the skull of the newborn infant which is characterized by multiple defects of the inner table of the vault. The defects may be present in any part of the calvarium but most frequently occur in the parietal and frontal bones. They vary in size, shape, and number. At post-mortem examination of such a skull, the outer table is often found to be complete with the lacunae being present as shallow depressions of the inner part of the vault. Hartley and Burnett¹ called this cranio-lacunaria in contradistinction to craniofenestria where the depressions are so deep that only a parchment-like membrane consisting of dura and periosteum is present. The distinction is not absolute, for some cases of cranio-lacunaria show minor tendencies toward fenestration whereas some cases of craniofenestria have to a certain extent changes of the lacunar type. Some of the defect areas are often so large that the cranial contents may bulge through them. Lacunar skull is usually but not invariably associated with spina bifida, encephalocele, meningocele, or myelocele. Other congenital developmental anomalies such as deformities of the ribs and extremities, cleft palate, mongoloid facies, microcephalus, and craniostenosis may be present. Hydrocephalus often occurs and may be progressive.

In the German literature this condition is known under the names of Lückenschädel, Leistenschädel, and Blasenschädel.

HISTORY AND ETIOLOGY

The first cases of lacunar skull were described in the late nineteenth century. West,² an Englishman, in 1875 gave the first authentic case report. Engstler,³ in 1905, reviewed the German literature on the subject. Kassowitz, in 1880, Wieland,⁴ in 1909, Cohn,⁵ in 1924, Faust,⁶ in 1931, and Ottow,⁷ in 1941, discussed the condition in extenso.

The first case in the American literature was reported by Markoe⁸ in 1907. Other case reports followed by Kerr¹⁰ in 1933, Maier¹¹ in 1934, Doub and Danzer¹² in 1934, Rothbart¹³ in 1936, Shearer⁹ in 1937, Dorrance¹⁴ in 1940, and Bettinger¹⁵ in 1942.

The etiology has been widely discussed. No entirely satisfactory explanation has been found. Some authors ascribed the condition to rickets.^{4, 16} Various authors thought that it might be caused by increased intrauterine, intracranial pressure.^{7, 15}

Rothbart¹³ incriminated a primary disturbance in the development of the membranous bones of the cranium produced by ischemia, as well as an increase in intrauterine, intracranial pressure leading to pressure atrophy. Any condition permitting firmer contact between the brain and the skull produces ab-

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normal pressure on the inner vault. If there is also increased intracranial pressure, the atrophy will be more marked.

Hartley and Burnett^{17, 18} did not find any constant relation to diseases such as syphilis, rickets, or toxemia of pregnancy; nor the presence of any causative abnormal pressure effect either within or without the skull, before or during birth. They feel that the condition may be due to a developmental defect in which two processes are frequently associated, namely, the faulty ossification of the primitive membranous vault which surrounds the early brain, and the faulty chondrification of the vertebral bow of the primitive membranous spinal column which surrounds the early spinal cord. This may be due to an inherent defect of a chromosomal nature in which unhealthy mesodermal tissue is produced.

INCIDENCE

Vogt and Wyatt¹⁹ reported on 6,000 skull examinations that were done on newborn infants of the Infants' and Children's Hospital in Boston. Craniolacunia occurred in 43 per cent of the 120 patients with meningocele. Two cases of true craniolacunia were found in over 5,000 cases without meningocele. Craniolacunia was least frequent in the presence of the smaller meningoceles and most frequent in association with the thoracic meningoceles. Its incidence in cases of meningocele was otherwise unaffected by the size or the location of the meningoceles. It was found more frequently in association with myelomeningocele than with simple meningocele.

Hartley and Burnett¹⁷ in Great Britain encountered twenty-eight cases in 3,828 newborn infants, giving an incidence of .94 per cent. Ten examples of craniolacunia were discovered in 232 radiographs of pregnant women, giving a radiological incidence of 4.3 per cent in antenatal cases (while in the material from which they collected, only three cases of craniostenosis were observed). Sixteen of the twenty-eight cases were primigravidas.

Ingraham and Scott,²⁰ in 1943, reported that the majority of their twenty patients with Arnold-Chiari malformation (this is a congenital malformation of the hind brain) showed craniolacunia.

DIAGNOSIS

Clinically, lacunar skull may be suspected, but the diagnosis usually rests on the roentgenographic appearance. There is a general diminution in thickness and delay in ossification in all of the flat bones of the skull as compared with the development of the skull of a normal infant. The sutures and fontanels may be widened. The most striking feature is the variation in density of the flat bone of the skull. Multiple areas of rarefaction are apparent, producing a "soap-bubble" or "honeycomb" effect. If there is only partial thinning, the diagnosis is more difficult. It can be differentiated from accentuated convolutional impressions due to markedly increased intracranial pressure as occurs in cases of craniostenosis, oxycephaly, scaphocephaly and brain tumor, by the contour of the skull which is more clearly demarcated in the latter. The lacunae are differently spaced than cerebral gyri and form a reticular, arborizing pattern.

The hydrocephalic skull at differential diagnosis must be approached with care. The less defined pattern of craniolacunias may be completely masked because the bones are thin and the cranial contents excessive. Craniolacunias can be differentiated from erosions caused by the granulations of Pachioni, syphilitic perforations, cleidocranial dysostosis, Hand-Schüller-Christian disease, and craniotabes with little difficulty.

Hartley and Burnett^{1, 17} discuss the advisability of antenatal radiological study, especially in cases of hydramnion or hydrocephalus, and also where the mother gives a history of previous stillbirths or previous children born with defects or deformities.

When craniolacunia is present, the shadow cast by the vault of the fetal skull becomes modified. Instead of being bounded by a smooth and regular margin of even density, interrupted only at the sutures, this margin becomes of variable thickness and density and of irregular shape. In some places it may be duplicated, while at others it may be completely defective so that the position of the sutures is lost and sometimes the suggestion of a reticular pattern may be seen in the vault bones. Often spinal deformities are seen in association with these changes (Brailsford^{21, 22}).

It is emphasized by Hartley and Burnett that the diagnosis can only accurately be made in the lateral view by a study of the parietal areas, for in the frontal and occipital regions the bars invariably appear narrow and sharply defined because they are viewed tangentially. A feature which may contribute toward the diagnosis of craniofenestria occurs in those cases in which bulging of the cranial contents takes place through the fenestria. They suggest that many cases have escaped detection in the past because of the following reasons: (1) the failure of radiologists and obstetricians to realize the possibility of their antenatal recognition and to appreciate that they frequently occur in cases of spinal defect. This has meant that many infants have been sent for "x-ray of the spine" only and the skull has not been examined. (2) The association of hydrocephalus with craniolacunia has not been realized. Hence, few have considered it worth while having radiographs made, whether of living or, more particularly, of stillborn hydrocephalic infants. (3) There need be no clinical feature to suggest the necessity for radiological examination of the skull since the outer surface of the vault bones may be smooth, and the sutures and the fontanels may be normal.

PROGNOSIS AND THERAPY

The prognosis is dependent on the general state of health and associated defects. Usually the infant dies from progressively increasing hydrocephalus or intercurrent infection, especially meningitis. Some authors have the impression that there are cases in which the craniolacunae gradually become less prominent.²³

The comparison of the clinical results of operation in cases of meningocele with and without craniolacunia was shown by Vogt and Wyatt.¹⁹ It was evident that the patients with craniolacunia did more poorly than those without these lesions. Good results were obtained in only two patients (4 per cent) of

the group with craniolacunias; whereas, 17 patients (25 per cent) of the group without craniolacunias had good clinical outcomes. All of the patients in whom good results were obtained had simple meningoceles, with the exception of two, neither of whom had craniolacunias. Progressive hydrocephalus was one of the most serious complications encountered in patients with meningocele. It was present in 48 per cent of the patients with craniolacunias and in 25 per cent of the patients without this lesion.



Fig. 1.—Lateroposterior view of baby H on the second day of life.

CASE REPORT

Baby H. was delivered by cesarean section from a 40-year-old white primigravida with negative Wassermann. Cesarean section was performed because of a large uterine fibroid. An x-ray taken five weeks before delivery showed that the head of the fetus was enlarged. Increased lordosis was noted but was thought to be due to an excessive amount of amniotic fluid. The weight of the infant at birth was 7 pounds, 4 ounces; length, 19 inches; circumference of the chest was 13 inches with the anteroposterior diameter slightly increased. The head was very large, measuring 15 inches in the occipitofrontal plane. The cranial bones were floating and their outlines easily palpated. Fine ridges were felt in the cranial bones especially in the occipital and parietal region. Soft areas were palpated over the entire skull. Some of the gaps in the parietal bones were so large that one could feel the dura protrude

through them (Fig. 1). The baby had a normal cry and the color was good. There was a defect, measuring 4 by 6 cm., in the central portion of the thoracolumbar region. The defect appeared red in color and slightly depressed, and in its upper two-thirds was covered by a transparent membrane which was continuous with the skin of the back. A white, bandlike structure which was slightly expanded in the central portion was thought to represent the spinal cord. The defect described felt mushy on palpation. Motion of the left leg appeared definitely decreased from normal. The right leg showed no impairment of function. The Moro embrace reflex was present. No ankle clonus or any other pathological reflexes could be demonstrated.



Fig. 2.—Spine and skull after post-mortem exposure.

X-Ray Findings.—The cranial bones were extremely thin with thicker ridges running through them in a network, giving the appearance of multiple holes (Fig. 3). The suture lines were very wide. The spine showed congenital abnormalities, particularly in the lumbar area where several hemi-vertebrae were noted and a marked spread of the laminae was present, consistent with a very extensive spina bifida.

Subsequent Course.—The skull increased gradually in size. The protrusion of the dura through the defects in the skull became more marked. The lesion of the back, previously described, which was slightly depressed at birth, began to bulge by the second day and seepage of the spinal fluid was noted. The area became markedly ulcerated. The subsequent course was downhill. The seventh day diarrhea and regurgitation became prominent. Hyper-

pyrexia occurred at the ninth day, and the baby died on the eleventh day with convulsions and other signs of meningitis.

Autopsy Findings.— (Autopsy performed by Dr. Jesse B. Helfrich.) After the dissection of the scalp, the bony plates were seen and found to be extremely thin. Multiple defects, mostly oval-shaped, some of them surrounded by thick, sharp, bony ridges, others by thin, flat ones, were visible and only covered by a translucent membrane consisting of dura and peri-



Fig. 3.—X-ray of the skull on the first day of life.



Fig. 4.—Transilluminated fragment of the dried skull.

osteum. There was a lacework of bony ridges visible at the interior aspect of the skull. The accompanying photographs are self-explanatory (Figs. 2 and 4).

After the brain was removed, a great amount of fluid escaped and the very thin brainy substance collapsed. Marked hydrocephalus was present. The choroid plexus was purple, covered with a purulent exudate.

In the middle of the back there was seen an oval area of necrotic skin through which the spinal fluid was exuding. The spinal fluid was light amber in color and purulent. After the skin of the dorsum was dissected away, the lower thoracic and all of the lumbar vertebrae were seen to be broadened. The spinal cord floated on the surface. It was yellowish in color and appeared infected. The chest and abdominal organs did not show any noteworthy changes.

SUMMARY

A case of craniolacunia of the newborn with spina bifida and meningo-myeleocele is discussed. A brief review of the literature is given.

Pictures were taken through the courtesy of Louis Lee and Robert C. Rieke.

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DISPLACEMENT OF THE MEDIASTINUM DUE TO PULSION BY A CASEOUS TUBERCULOUS LUNG WITHOUT PLEURAL EFFUSION

REPORT OF A CASE IN AN INFANT

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IN A review of standard texts of physical diagnosis, clinical tuberculosis, roentgenology, and the available periodical literature no mention of mediastinal shift due to pulsion by a caseous lung without the presence of pleural effusion was found. Displacement of the mediastinum *toward* the affected side due to pulling of the mediastinum by adhesions and scars of the lungs and pleura in chronic tuberculous or nontuberculous infection is a well-known phenomenon.¹ Displacement may also be brought about by atelectasis from tuberculosis or other cause² or, on occasion, by an acute nontuberculous pneumonia.³ Compensatory emphysema of the nondiseased lung in unilateral pulmonary infection may act as an agency in these mediastinal displacements.⁴ In all these instances the displacement is toward the diseased lung.

Intrapulmonic disease processes capable of causing contralateral or pulsion displacement are tumor of the lung,⁵ cystic malformations of the lung,⁷ and unilateral emphysema.⁸ Unilateral emphysemas not only may be compensatory, as mentioned, but also may be due to partial bronchial obstruction or have no discoverable cause.⁸

Several extrapulmonary causes of contralateral displacement of the mediastinum should be mentioned: pleural effusion, pneumothorax, unilateral diaphragmatic paralysis, and masses such as intrathoracic goiter or diaphragmatic hernia protruding into the chest cavity. The most frequent and most important cause of pulsion of the mediastinum is, of course, pleural effusion.

CLINICAL DATA

An 8-month-old mestizo boy entered the hospital with a complaint of "noisy breathing."

The present illness started about three months before admission with what the mother referred to as "asthma," characterized by heavy breathing but no cough. Fever then developed. The patient was treated in another hospital with sulfathiazole and was discharged after ten days improved. The mother was told that the infant had pneumonia of both lungs and pleurisy. Eight days after discharge, however, the symptoms recurred and persisted. Fifteen days before admission to this hospital he had developed swellings over the skin of the head and back. Ten days before admission, diarrhea and vomiting started and he began to cough. During this three months' period he lost much weight.

Physical examination showed a malnourished, slightly dehydrated, feverish, acutely and chronically ill baby lying in bed with his head retracted. Over the skin of the head, neck, and trunk were numerous dull red, fluctuant swellings about 1.0 cm. in diameter. The anterior fontanel was depressed. The neck was stiff. The alae nasi were dilated; breathing was labored and shallow. There was ballooning of the intercostal spaces on the left, and the left side of the chest was more expanded than the right. The apex beat of the heart was observed and felt in the costal angle. Percussion of the heart borders was not satisfactory but the heart beat was heard loudest over the sternum. There were no murmurs and the quality of the heart sounds was good. The entire left side of the chest was flat to percussion; breath

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sounds were absent over the entire left lung. The right side of the chest was normally resonant. There were no râles or abnormalities of breath sounds. Both the spleen and the liver were enlarged to three fingerbreadths below the costal margins. The abdomen was moderately distended but peristalsis was heard on auscultation. The reflexes were essentially normal.

Laboratory Data.—Urinalysis was negative except for 2 plus albumin. The stool was formed, yellow, and a preparation of unconcentrated specimen stained by Ziehl-Neelsen's technique showed many acid-fast bacilli. The blood contained 8 Gm. of hemoglobin per 100 c.c.; erythrocytes 2,750,000 per cubic millimeter; leucocytes 8,200 per cubic millimeter with neutrophils 73 per cent and lymphocytes 27 per cent. No malaria parasites were present.

Roentgenogram of the chest on admission (Fig. 1) was reported as follows: "Massive pleural effusion, left, which displaces the heart and mediastinum to the right."



Fig. 1.—Note shift of the mediastinum to the right.

Course in the Hospital.—Thoracentesis of the left hemithorax was done on the day of admission. There was no ready flow of fluid through the needle. On exerting negative pressure, however, about 0.5 c.c. of thick, white, caseous material was withdrawn. This material showed a myriad of acid-fast bacilli on smear but was free of other organisms both by smear and culture; only a few cells were present, all monocytes. A lumbar puncture yielded clear fluid with normal dynamics. Pandy's test showed increased globulin but only one lymphocyte per cubic centimeter was present; no pellicle formed on standing. The patient ran a steadily downhill course, with an irregular, intermittent fever between 99 and 103° F. and died a week after admission.

AUTOPSY FINDINGS

Complete autopsy was done eighteen hours after death. The anatomic diagnoses included:

1. Lobar pneumonia, tuberculous, left lung, with marked enlargement and with extensive diffuse caseation necrosis of practically the entire organ.

2. Tuberculous pleuritis, left, with obliteration of left pleural cavity.
3. Mediastinal shift to the right, pulsion in type, due to enlargement of the left lung.
4. Bronchopneumonia, right lung, tuberculous, slight, with caseation necrosis.
5. Tuberculosis, caseous, of cervical, mediastinal, and abdominal lymph nodes.
6. Tuberculous ulcers of ileum, cecum, and colon.
7. Multiple tubercles of liver, spleen, and kidneys.
8. Tuberculosis of right middle and inner ears with involvement of petrous portion of right temporal bone.
9. Pyogenic abscesses of skin, *Streptococcus hemolyticus*.
10. Emaciation.

Detailed description may be limited to the thorax. Upon removal of the anterior thoracic wall it was observed immediately that the trachea, heart, and mediastinum were shifted to the right. The apex of the heart was in the fifth interspace 2.0 cm. to the left of the midsternal line and pointed downward rather than laterally. The right border of the heart was located 3.0 cm. to the right of the midsternal line. In other respects the organ was not remarkable.

The left pleural cavity was completely obliterated by dense fibrous adhesions between the visceral and parietal surfaces; *no free fluid was present*. The left lung was markedly enlarged, weighing 400 grams (normal weight 45 grams⁹). This enlargement had distended the left hemithorax and had caused a displacement of the mediastinum to the right. Upon external examination the entire organ was firm, tense, and apparently completely consolidated. Prominent rib markings or indentations were present on the surface of the lung. Sectioning revealed that virtually the entire parenchyma was one solid mass of white or yellowish white, nonaerated, caseous material hardly recognizable as pulmonary tissue. Only at the apex was there a small amount of parenchyma which, although consolidated, had not been completely destroyed by caseation necrosis. No cavities were present.

The right pleural cavity contained 10 c.c. of pink fluid. Only a few flimsy adhesions were present between the visceral and parietal pleurae at the apex of the right lung. The right lung weighed 120 grams (normal 52 grams⁹) and was not atelectatic. Scattered uniformly in all lobes were tiny tubercles. In addition, areas of caseation necrosis averaging 1.5 cm. in their greatest dimension were present in the upper and middle lobes. The intervening soft pink parenchyma occupied approximately one-half of the lung. There was no fibrotic process of either the right lung or right pleura which conceivably could have drawn the mediastinum to the right.

Much of the mucosa of the bronchi was necrotic. The peritracheal and peribronchial lymph nodes were markedly enlarged and consisted of masses of caseous material contained within thin, tense capsules. One such node was in intimate contact with the left main stem bronchus at the site of necrosis both of the mucosa and the wall. It appeared likely that rupture of caseous material into the bronchus may have occurred in this area.

MICROSCOPIC EXAMINATIONS

Several sections of the left lung were similar. The pleura was widened by fibrosis and infiltrated by lymphocytes and epithelioid cells, but no well-defined tubercles or giant cells were present. Within the parenchyma proper the histologic changes were so extensive that the tissue could scarcely be recognized as lung. In large areas the alveolar architecture was completely obscured and represented merely by zones of confluent, early caseation necrosis. Here and there, however, could be recognized a few pulmonic alveoli, the lumina of which were filled with fibrinopurulent or caseous exudate. Some of the caseous zones appeared to have undergone dissolution with the formation of irregular spaces. Nowhere were found well-defined tubercles with epithelioid rims and giant cells. It was felt that the lesion of the left lung was a tuberculous pneumonia showing no resolution but conversion into caseous parenchyma.

Scattered within the pulmonary parenchyma of the right lung were many small patches of caseation necrosis. The intervening parenchyma contained alveoli filled with serous or purulent exudate in which many mononuclear cells were present. As in the right lung, no well-formed tubercles were seen and giant cells were absent. Much of the mucosa of the

bronchi and bronchioles was necrotic and their lumina contained purulent or caseopurulent material. In smears of both lungs and of the lymph nodes a large number of acid-fast bacilli morphologically similar to tubercle bacilli were present.

DISCUSSION

The chief interest in this case lies in the similarity of the clinical and roentgenologic findings with those of pleurisy with effusion. Flatness to percussion, absence of breath sounds over the entire left side of the chest, and displacement of the heart to the right were considered diagnostic of effusion in the left pleural cavity. Furthermore, the left intercostal spaces bulged and the left side of the chest was splinted and fixed in a way usually characteristic of fluid. The roentgenogram showed homogeneous opacity over the entire left side of the chest with the heart and trachea shifted to the right. This seemed to confirm the clinical diagnosis of effusion.

It is questionable if the differential diagnosis could have been made before the thoracentesis. Grocco's triangle of dullness might have been a helpful sign in an older patient but is of little, if any, value in infants. Major states "the 'feel' on percussion and the note obtained (in pleural effusion) are different from the dullness obtained in consolidation of the lung."⁶ No difference was detected in this case. The almost complete absence of air-containing alveoli produced an absolute dullness or flatness indistinguishable from the percussion note over massive effusion.

After the thoracentesis it was clear that some condition was present other than simple tuberculous pleurisy with effusion. The failure to obtain a free flow of fluid and the recovery of a small amount of tuberculous caseous material on suction indicated that either a caseous empyema was present or the needle was in the lung. Of these two possibilities, the first seemed the more likely in view of the mediastinal shift. Only after the thorax was opened post mortem was the actual situation correctly evaluated.

SUMMARY

A case of pulmonary tuberculosis in an infant is presented in which the caseous lung enlarged sufficiently to displace the mediastinum toward the other side. The clinical and roentgenologic findings closely resembled those of pleurisy with effusion.

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AGENESIS OF THE LUNG

CASE REPORT

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CONGENITAL failure of development of one or several lobes of the lung is a rare anomaly. Unless complications arise as a result either of other anomalies or of other diseases few cases are diagnosed prior to death, for their courses may be symptomless.

CASE REPORT

An 8-month-old white female was seen in the Out-Patient Clinic on March 30, 1945.

The baby was born of normal parents on Aug. 7, 1944. Delivery was uneventful, and the child cried spontaneously without any respiratory embarrassment. Growth and development occurred normally without signs of respiratory difficulty or feeding disturbances.

The baby was brought in because of fever and anorexia of twenty-four hours' duration. Physical examination revealed the following salient features: The temperature was 103° F.; pulse, 110; and respirations, 28. The child's throat and tonsils were red, nose congested, and both eardrums injected. Examination of the chest presented the most striking signs. The entire left side including the usual cardiac area was hyperresonant to percussion, and breath sounds were exaggerated. Conversely, on the right, percussion was impaired and breath sounds suppressed. The apex beat could be palpated in the fourth interspace just to the right of the sternum. Cardiac sounds were best heard on the right side of the chest. No abnormal heart tones or murmurs could be elicited. The remainder of the physical examination revealed no abnormalities.

Following recovery from the upper respiratory infection, the child appeared well. Chest signs remained unchanged.

X-ray examination of the chest confirmed the physical findings. The left lobes appeared unusually clear, probably as a result of compensatory emphysema. The heart seemed to occupy most of the right chest. Very little lung could be discerned on the right side. Intercostal spaces were wider on the left. By fluoroscopy it could be seen that the heart was shifted over to the right without apparent rotation. Barium mixture given by mouth indicated that the esophagus was displaced to the right. Both diaphragms were mobile with much greater excursions on the left. (Figs. 1 and 2.) X-rays of the remainder of the skeletal system revealed fusion of the eighth and ninth dorsal vertebra and lumbarization of the first sacral segment.

Electrocardiograms revealed the following: A sinus tachycardia was present. Deep waves measuring up to 15 mm. in depth occurred in Leads I and II. R waves measured 17 mm. in these leads. A small S₂ was present. All P and T waves were normal and upright. There was no evidence of a true congenital dextrocardia.

Bronchoscopy was accomplished by Dr. G. B. Ferguson. Increased secretions and poor tolerance of the child to the procedure did not permit a clear picture of the situation through the bronchoscope. However, as a result of the entrapment of air both the trachea and left bronchus could be clearly visualized by x-ray. The right bronchus could not be seen.

From the Medical Service, Station Hospital, Seymour Johnson Field.



Fig. 1.—X-ray chest in upright position. (Positive film.) (Official photograph, U. S. Army Air Forces.)

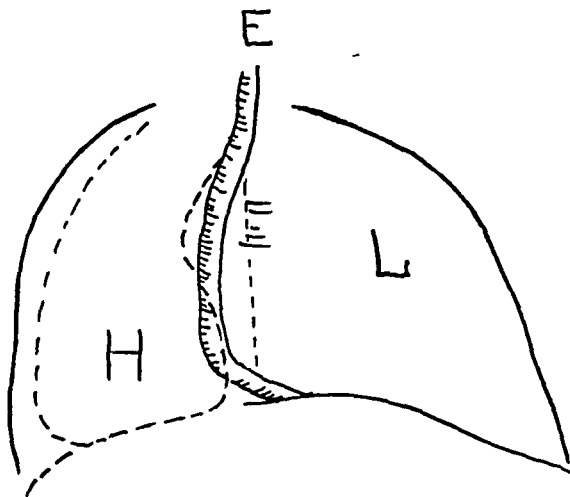


Fig. 2.—Diagram of x-ray and fluoroscopy findings *H*, heart; *E*, esophagus; *L*, left lung. (Official photostat, U. S. Army Air Forces.)

COMMENT

Reviews on the subject have been presented by Killingsworth and Hibbs¹ and later by Valle and Graham.² A total of forty-one cases has been recorded. Of these, twelve patients were over 19 years, and four ranged from 41 to 72 years in age. Only four cases were diagnosed during life. In previous cases the left lung was affected twice as often as the right. The anomaly varied from complete aplasia with absence of the bronchus and vascular supply to hypoplasia of the lung associated with a bronchus reduced in size. Mediastinal structures were displaced toward the involved side, and the remaining lung underwent compensatory emphysema. Other congenital anomalies were frequently present. In uncomplicated cases symptoms ranged from lack of complaints to dyspnea, cyanosis, stertorous breathing, and/or developmental failure. In many patients difficulties arose from associated anomalies or from pulmonary infections such as pneumonia or bronchiectasis. The physical signs and x-rays were often mistaken for massive or fetal atelectasis. The final diagnosis can be made only by exploratory thoracotomy.

In this case, the diagnosis of agenesis of the right lung was made from the clinical picture and the radiographic studies, which agreed with the description by Caffey.³ The lack of respiratory tract symptoms and the absence of asphyxia at birth indicated that in the prenatal period an anomaly of the right lung developed and was compensated by hypertrophy of the remaining pulmonary tissue.

SUMMARY

A case of agenesis of the right lung in an 8-month-old infant is reported. The diagnosis was made during life and was based upon the lack of respiratory symptoms associated with extremely abnormal radiographic findings in the chest.

The authors are grateful to Dr. G. B. Ferguson of the McPherson and Duke Hospitals, Durham, North Carolina, for assistance in study of this case.

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ATELECTASIS OF THE NEWBORN: TREATMENT BY BRONCHOSCOPIC DRAINAGE

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A TELECTASIS of the newborn has always been a serious condition and one which has been very difficult to treat. Unfortunately the usual conservative measures in treatment are often inadequate, and the infant frequently expires of exhaustion.

We wish to present the procedure of bronchoscopic aspiration as an adjunct in the treatment of severe cases of congenital atelectasis due to obstruction of the bronchi with body secretions. Working independently, we have performed this procedure on twenty-three infants, and we feel the results have been quite gratifying.

Woodward and Waddell¹ presented five cases of atelectasis in newborn infants and cited seventeen other cases of Dr. Maurice G. Buckles that were treated by bronchoscopic aspiration. This article stimulated the interest of pediatricians in our locality, so that we have been asked to perform bronchoscopy on twenty-three patients who had not responded to conservative therapy and in which exhaustion of the infant seemed inevitable.

According to Brennemann,² in intrauterine life the child's lungs are atelectatic. Twenty minutes after birth there is a 17 c.c. air capacity, and from three to six hours after birth the capacity is about 36 c.c. Normally it is several days before the lungs have completely expanded. This expansion becomes complete first in the anterior borders and apices. The paravertebral, central, and posterior portions are the slowest to expand.

Wilson and Farber³ feel lack of expansion in premature infants is not a failure of respiratory effort in many instances, although this may be weak, but that it is due to cohesion of moist surfaces of the air passages. This condition may, of course, be emphasized by any disturbance in the respiratory center, imperfectly developed thoracic mechanism, or through obstruction of bronchi by aspiration of amniotic fluid, mucus, or blood.

Patterson and Farr⁴ present strong evidence in support of the hypothesis that the human fetal respiratory tract is not inert in utero, but is subject to rhythmic respiratory movements, during which there is a tidal flow of amniotic fluid through the bronchial tree and alveoli. Examination of lung secretions in cases of neonatal deaths, some in stillborn infants, showed amniotic fluid present. That this is not entirely due to passage through the birth canal, as is generally thought, is shown by the fact that some of these infants were delivered by cesarean section. Snyder and Rosenfeld⁵ showed that India ink injected into the amniotic sac is followed shortly by the appearance of this material in the pulmonary alveoli of the animal fetus.

To date we have used bronchoscopy in twenty-three cases with eight deaths, representing a mortality of 34.7 per cent. In these eight cases that ended un-

favorably, the diagnosis of true congenital atelectasis due to bronchial obstruction was not established with certainty prior to bronchoscopy. With some hesitancy, however, the cases were bronchoscoped only to reveal little bronchial secretion. Subsequent post-mortem examination revealed that only two of the eight deaths were due to true atelectasis and the remaining six cases were found to include cerebral hemorrhage, congenital aplasia of the brain, diaphragmatic hernia, pneumonia, congenital heart and massive patchy atelectasis not due to bronchial obstruction. The corrected mortality rate, after these complications were eliminated, would be two deaths in seventeen cases of true atelectasis, or 11.7 per cent.

In view of our experience in these instances, we feel it is imperative prior to bronchoscopy to rule out by every means at our disposal the various pathologic entities that may resemble congenital atelectasis due to bronchial obstruction. These include asphyxia, congenital disease of the heart and blood vessels, congenital cystic lung, cerebral trauma, blood dyscrasia, pulmonary infection, diaphragmatic hernia, and congenital fetal atelectasis.

Careful examination of the infant's respiratory rate and rhythm will aid in eliminating distress due to cerebral injury.

X-ray studies should be made prior to bronchoscopy in all cases. This, together with physical examination of the child, will aid in eliminating congenital heart, congenital cystic lungs, diaphragmatic hernia, pulmonary infection, and congenital fetal atelectasis due to patchy, nondeveloped lung areas.

Bronchoscopic aspiration is indicated in any case of congenital atelectasis due to bronchial obstruction which has failed to respond to the usual methods of conservative treatment. It is not advisable to wait for signs of exhaustion before bronchoscopy is performed. The interval of time that it is safe to wait obviously depends on the extent of the atelectasis and the infant's physical condition. Most of these cases are encountered in premature infants whose reserve stamina is, indeed, very limited.

In all cases, some secretions have been aspirated from the bronchial tree. However, in only one case was a definite thick, stringy plug of exudate removed from a single bronchus. If cohesion of surfaces tends to promote atelectasis, perhaps instrumentation helps to relieve this condition.

Following bronchoscopic aspiration there is usually a progressive improvement in the infant's respiration. However, complete relief most frequently occurs from six to eight hours after instrumentation. This is apparently due to removal of secretions from the larger bronchi allowing the smaller terminal branches to drain.

The classical picture of congenital atelectasis secondary to bronchial obstruction is herein presented:

1. Progressive dyspnea with cyanosis, most marked after crying or other effort. This may often be temporarily relieved with oxygen. When these symptoms are not present, listlessness and pallor are usually noticed.

2. Suprasternal retraction with diaphragmatic tug on the lower ribs and diminished thoracic expansion on one or both sides, associated with suppressed breath sounds with or without percussion dullness.

3. Coarse inspiratory râles and areas of localized emphysema. *Coarse moist râles are an important finding and are usually absent in cases not due to obstruction from body secretions.*

4. Dehydration.

5. X-ray of the chest will usually show a rather complete atelectasis of one or more lobes. An x-ray should be made when possible in every case, but the diagnosis is made primarily on the clinical picture.

Congenital atelectasis most commonly occurs in premature infants. In our series, nineteen of the twenty-three cases bronchoscoped were in this category, representing 82.6 per cent. The smallest infant treated was a twin weighing 4 pounds, 4 ounces. Another, weighing 4 pounds, 7 ounces and seven weeks' premature, was likewise bronchoscoped, and in both instances the infants went on to normal development.

The procedure of bronchoscopy seems to produce little, if any, shock to these babies. Likewise, laryngeal edema does not develop secondary to instrumentation. This is due to two factors. First, the length of time consumed in the procedure is less than four minutes. Second, the type of bronchoscope used produces little trauma to the glottic chink.

The bronchoscope used in our series is the new, improved 3 mm. bronchoscope as devised by Dr. Simon Jesberg, of Los Angeles, and described by him in the 1941 *Archives of Otolaryngology*.⁶ The Jesberg bronchoscope has the same inside diameter, but the outside diameter is one millimeter smaller than the standard 3 mm. bronchoscope usually used, measuring 4.5 mm. by 5 mm. This millimeter is gained by using a smaller light carrier and light bulb. The tip of the bronchoscope is likewise much smaller than the standard bronchoscope. Consequently, this instrument passes with little difficulty through the smallest glottic chink and subsequent laryngeal edema or shock is prevented.

CONCLUSIONS

1. The etiology of atelectasis of the newborn is not fully understood.
2. Selected cases of congenital atelectasis secondary to bronchial obstruction, which fail to respond to conservative treatment, are materially benefited by bronchoscopic aspiration.
3. Bronchoscopic aspiration of the newborn infant is relatively a benign procedure when properly performed.
4. The improved 3 mm. Jesberg bronchoscope is strongly recommended for use in these cases.

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LISTERELLA MENINGITIS

REPORT OF A CASE WITH RECOVERY

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H. T. KNIGHTON, D.D.S.
LOUISVILLE, KY.

L*ISTERELLA monocytogenes* is a rare pathogen for man. A review of the literature showed it to be extremely rare as a cause of meningitis in infancy. Burn¹ (1936) reported three fatal cases of *Listerella* infection in infancy, one of which at autopsy revealed extensive suppurative meningitis. Carey² (1936) reported a case of acute meningitis caused by *L. monocytogenes* in a small child with recovery. Poston, Upchurch, and Booth³ (1937) reported a fatal case in a 3-year-old child. In 1939 Porter and Hale⁴ mentioned an unpublished case of a small boy with *Listerella meningitis* treated successfully with sulfanilamide. Wright and MacGregor⁵ (1939) reported a fatal case of *L. meningitis* in a 17-month-old infant. A complete review of the literature on listerellosis has recently been published by Kaplan⁶ (1945).

We wish to report a case in an infant treated with sulfadiazine and penicillin with recovery.

CASE REPORT

History.—W. L. R., a 6-week-old male infant from Defoe, Ky., was admitted to the Children's Free Hospital of Louisville, Ky., on April 26, 1945. The chief complaints were fever and irritability. The infant was in excellent health until the morning prior to admission at which time he became irritable with a fretful cry; later in the day he developed fever. No vomiting, diarrhea, cold, or cough were noticed. The child lived on a farm. The livestock consisted of chickens, swine, and cows. The parents stated that the animals were in excellent health at the present and there was never any disease prevalent in the stock. The past history and family history were noncontributory.

Physical Examination.—The patient was an acutely ill, irritable male infant in constant motion and crying continuously; the rectal temperature was 103.4° F. The skin was hot and dry with a few vesicular and pustular lesions over the face. The anterior fontanel measured 4 cm. by 4 cm. and was quite tense and bulging. Aside from this there were no signs of meningeal irritation. The lips were cherry red and dry. The reflexes were normal.

Laboratory Findings.—Lumbar puncture on admission revealed a cloudy spinal fluid under normal pressure with immediate formation of fibrin strands. The white cell count of the spinal fluid was 7,400 per cubic millimeter with 94 per cent polymorphonuclear leucocytes and 6 per cent lymphocytes; globulin was 3 plus, and sugar was under 30 mg. per cent.

On primary smear a gram-positive rod was seen which grew on culture and was subsequently identified as morphologically resembling *L. monocytogenes*. A blood culture obtained on the day of admission revealed *Bact. alkaligenes* which was thought to be a contaminant.

A repeat lumbar puncture on the second and third days again revealed on smear and culture a gram-positive rod. Four subsequent lumbar punctures were all negative on both

From the Department of Pediatrics, the Services of Drs. James W. Bruce and W. W. Nicholson, and the Department of Bacteriology, University of Louisville School of Medicine.

smear and culture. The spinal fluid white blood cell count, sugar, and protein gradually returned to normal.

The white blood cell count was 21,000 per cubic millimeter on admission, 14,000 per cubic millimeter on the thirteenth day and 16,000 per cubic millimeter on the fifty-fourth hospital day (three days prior to discharge). A red blood cell count was 3,850,000 per cubic millimeter on admission, 2,540,000 per cubic millimeter on the eighth hospital day and 3,800,000 per cubic millimeter on the fifty-fourth hospital day. The hemoglobin was 12.5 Gm. per 100 c.c. of blood on admission and the same on the fifty-fourth hospital day. Blood sulfadiazine levels ranged from 7.8 mg. per cent to 25.8 mg. per cent during the first week of hospitalization. The initial urinalysis revealed 4 plus albumin, but all subsequent urinalyses were negative. The blood Kahn and tuberculin tests were negative.

Treatment.—The infant was immediately given 10,000 units of penicillin intrathecally and 15,000 units intramuscularly. This was followed by 5,000 units of penicillin every three hours intramuscularly. The following day another 10,000 units was given intrathecally and the intramuscular penicillin was increased to 10,000 units every three hours, and on May 12 it was discontinued. The total amount of penicillin administered was 20,000 units intrathecally and 1,100,000 units intramuscularly. An initial dose of 20 c.c. of a 5 per cent sodium sulfadiazine solution was given subcutaneously followed by 100 c.c. of M/6 sodium lactate. This was followed by 15 c.c. of a 5 per cent sodium sulfadiazine solution every eight hours. A continuous intravenous infusion was started with 5 per cent glucose in distilled water. At the end of thirty-six hours this was discontinued and separate infusions were given intravenously and subcutaneously as needed to maintain body hydration. On May 2 the sulfadiazine administration was changed to the oral route, 0.25 Gm. every four hours for one week. Due to an upper respiratory infection the sulfadiazine was resumed May 17, 0.125 Gm. being administered every four hours for three days. On June 8, 1945, the child developed bronchopneumonia for which sulfadiazine, 0.125 Gm. every three hours, was given for five days, and penicillin, 5,000 units every three hours, was given intramuscularly for six days (total of 240,000 units).

Supportive therapy consisted of oxygen during the first week and repeated transfusions of blood and plasma as indicated during his hospital stay.

Course.—During the first week of hospitalization the infant was acutely ill with a temperature ranging from 98.6° F. to 105.2° F. The second week of illness the infant's febrile course subsided. At the end of the second week and the beginning of the third week the child cried constantly and required considerable sedation. Following this the course was uneventful except for an upper respiratory infection and bronchopneumonia of moderate severity. Both were adequately cared for by the chemotherapy.

During the first two weeks the child's weight dropped from 11 pounds, 9 ounces, on admission to 10 pounds, 14½ ounces. Following this the weight gradually increased to 13 pounds, 3 ounces, on the day of discharge, June 21, 1945, fifty-seven days after admission.

There were no apparent neurological changes; the child was bright, had normal reflexes, and was apparently in excellent health on discharge.

BACTERIOLOGY

The spinal fluid was streaked on blood agar and inoculated into Douglas broth and ascitic fluid agar. Growth appeared on all three of these media.*

Morphology.—The organism, isolated in pure culture from the spinal fluid, appeared as a small gram-positive rod. The average size was 0.5 by 1 to 2 microns but occasional larger forms were seen. In smears made from eighteen-hour broth cultures, the organisms were irregularly arranged except for a tendency toward parallel arrangement. Motility was evident in eighteen- to twenty-four-hour cultures. There was no evidence of branching or clubbing on any media. The organism was nonacid-fast, and failed to produce spores. There was no evidence of encapsulation.

*Original smears and isolations were made by Miss Anne Butorff, Bacteriologist in the Louisville General Hospital, Bacteriological and Serological Laboratories, Dr. James A. Kennedy, Director.

Cultural.—Growth was evident within twenty-four hours under aerobic conditions on both plain nutrient agar and blood agar. Forty-eight-hour colonies on blood agar were round, 1 mm. in diameter, and were surrounded by a definite zone of hemolysis.

Biochemical.—Acid, but no gas, was produced in glucose, salicin, and rhamnose within twenty-four hours. Similar reactions were produced more slowly in lactose, maltose, sucrose, dextrin, and galactose. There was neither fermentation of mannite, inulin, nor xylose. Tests for indole and hydrogen sulfide were uniformly negative.

Pathogenicity.—The organism was distinctly pathogenic for rabbits and mice. Intravenous injections of 0.5 c.c. of an eighteen-hour broth culture produced death within forty-eight hours in each of four rabbits injected. Intraperitoneal injections of 0.25 c.c. also produced death within forty-eight hours in two mice. One mouse and two rabbits were studied after death and pure cultures of the organism were isolated from the heart blood, lungs, liver, and spleen of each animal.

Histopathologic Sections Revealed.—*

Heart: Severe cloudy swelling only.

Lungs: Large portions of the lungs were consolidated by exudate consisting chiefly of serous fluid and a very small amount of blood. The bronchioles contained similar material and in some of them the epithelium was sloughing. There was an intense congestion; possibly this slight diffuse hemorrhage was chiefly secondary to the congestion. The leucocyte response was minimal and consisted of neutrophils and monocytes. There was no focal necrosis. There were numerous emphysematous blebs at the periphery.

Liver: There were great numbers of microscopic abscesses in various locations of the lobule. Necrosis was of the liquefaction type. The leucocyte response was chiefly neutrophilic; a great proportion of the cells were fragmented. There was no evidence of repair.

Spleen: The spleen was very badly damaged by serous exudate similar to that in the lung. There was much blood pigment in the reticulum. The cells were vacuolated and swollen so that the architecture was markedly distorted. Leucocytic infiltration was minimal and consisted of monocytes and neutrophils. The general appearance of the spleen suggested that it was necrotic.

Kidneys: Marked cloudy swelling only.

Lymph Nodes: The lymph nodes were badly damaged by abscesses similar to those in the liver except that there were more monocytes in the lymph nodes and a few giant cells.

Pancreas: Marked cloudy swelling.

Interpretation.—

1. Bronchopneumonia with emphysema
2. Multiple abscesses of lungs
3. Acute splenic tumor, marked
4. Suppurative lymphadenitis
5. Marked cloudy swelling of all viscera

Resistance to Penicillin.—In vitro tests for penicillin susceptibility were made similar to those reported by Foley, Epstein and Lee⁷ (1944). Serial dilutions of a commercially prepared extract of penicillin were made in 5 c.c. lots of sterile peptone water. Twenty-four-hour peptone water cultures of the gram-positive rods under study were diluted 1 to 10 with sterile 0.85 per cent sodium chloride solution. Similar dilutions were made of a twenty-four-hour peptone water culture of *Staphylococcus aureus* (previously tested for penicillin susceptibility). Dilutions of the penicillin in the peptone water (5 c.c. amounts) were inoculated with .05 c.c. of either *Staph. aureus* or the gram-positive rods isolated from the case herein reported.

The following results were recorded after twenty-four hours' incubation at 37° C. Only 0.02 unit per cubic centimeter were necessary to inhibit the growth of the *Staph. aureus*, while from 0.3 to 0.4 unit per cubic centimeter were necessary to inhibit the growth of the gram-positive rods. The in vitro resistance of these gram-positive rods to penicillin may, therefore, be estimated as from fifteen to twenty times greater than the resistance of the *Staph. aureus* strain.

*Dr. A. J. Miller, Department of Pathology.

SUMMARY OF BACTERIOLOGY

Based on these reactions, this organism appears to be similar to *L. monocytogenes* as described by Topley and Wilson⁸ (1936) in the second edition of their textbook. It is also similar to the organism described by Webb⁹ (1943). It differs from other reported reactions of strains studied by Webb (1943) in fermentation of galactose and from Bergey's¹⁰ (1939) description in its failure to ferment xylose. The organism's susceptibility to penicillin was approximately twice that reported by Foley, Epstein, and Lee⁷ (1944) for *Listerella* strains, but still approximately twenty times as resistant as was the *Staph. aureus* strain. However, it seems logical to conclude that the organism isolated from this patient's spinal fluid was a strain of *L. monocytogenes*.

DISCUSSION

Porter and Hale⁴ reported in 1939 that seventy-seven of eighty control mice infected with *Listerella* died, while fourteen of sixty treated with sulfanilamide died, and only two of twenty treated with sulfapyridine died. Foley, Epstein, and Lee⁷ in 1944 reported their results of experiments with several strains of *L. monocytogenes*. In comparison to other gram-positive organisms they found that *Listerella* grew freely in forty times the concentration of penicillin necessary to inhibit completely the growth of certain gram-positive organisms studied. In our studies we found the organism from fifteen to twenty times as resistant to penicillin as is the *Staph. aureus* (see section on bacteriology). It appears, therefore, that penicillin is not a potent bacteriostatic agent for this organism. In all probability the effective agent in the treatment of this case was sulfadiazine.

CONCLUSION

A case of meningitis in an infant caused by *L. monocytogenes* and treated with sulfadiazine and penicillin with recovery is herein reported.

Sulfadiazine may be the drug of choice in the treatment of *Listerella* infection but further studies will have to be made to reveal its value as a chemotherapeutic agent in the treatment of listerellosis.

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CONGENITAL ECTODERMAL DEFECT

REPORT OF AN UNUSUAL CASE INVOLVING SCALP AND LEG

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DURHAM, N. C.

ACCORDING to Anderson and Novy,¹ they made the first report in the American dermatologic literature in 1942 on congenital ectodermal defects of the scalp. They present four cases and an excellent review of the literature.

Ingalls,² in 1933, gave a complete report on the study of sixty cases regarding the pathology of development of congenital ectodermal defects of the scalp.

There are many theories of etiologic cause including amniotic adhesions, hereditary factors, arrested development, intrauterine healing of angioma, pressure necrosis of the extremities and of the scalp during labor. Ingalls, in his discussion of etiologic factors, states that there is a total lack of any evidence pointing to amniotic influences, except for one reported case. He believes the cause to be on a basis of inherent fundamental factors, which impress upon the midline of the head with a degree of sensitivity or vulnerability equaled perhaps nowhere else on the body. The investigations, clinical findings, and opinions of other authors generally agree with his.

Clinical characteristics are relatively consistent. The majority of the lesions are single and usually located in or near the midline and most commonly on the vertex. The size of the lesion averages 1 to 2 cm. and the largest reported lesion measured 60 sq. cm. The lesions are usually oval in configuration, only occasionally elongated or irregular. In a majority of cases only the epidermis and the subcutaneous tissues were involved. The lesion may extend to the dura, pericranium or glia. The gross features show considerable variations but are usually described as having sharp punched-out margins, with the lesion itself consisting of scarlike tissue. At first a dry translucent membrane covers the area and later breaks down leaving granulation tissue. Despite occasional variations in gross appearance, the absence of hair tends to be a consistent feature.

Eight per cent of the cases reported have been associated with a congenital defect elsewhere.²

The diagnosis is based on the aforementioned criteria being present at birth. In the differential diagnosis criminal injury, forcep injury, primary syphilis, and congenital depression of the skull are to be considered.

Prognosis is less favorable for scalp defects than for ectodermal defects elsewhere because of the danger of increased injury to the lesion during delivery. There has been a 20 per cent mortality rate with most of the deaths at least partially referable to the lesion on the scalp.²

From the Division of Dermatology and Syphilology of the Department of Medicine, Duke University School of Medicine.



Fig. 1.



Fig. 2.

There seems to be no treatment indicated except the prevention of trauma and secondary infection by the use of local bland therapy.

REPORT OF A CASE

B. C., female aged 3 weeks, was first seen April 6, 1945, because of a lesion on the scalp and left leg. The mother and father had negative Wassermann serologic reactions on their peripheral blood. No history of development of abnormalities in the offspring of either maternal or paternal families could be obtained. The labor of the mother and the delivery of the child, without forceps, were normal. The infant was normal in every way except for the skin lesions.

On examination there was present a lesion on the right vertex, which was 8 by 6 cm. in size (Fig. 1). The lesion was covered by a transparent membrane. Scar tissue was present along the borders of the affected area. The left leg showed a similar lesion that formed an encircling band about the ankle, 3 cm. in width (Fig. 2). Both lesions showed atrophy, especially on the ankle where there was some deformity due to fibrosis and scarring. The lesions were treated with a simple boric acid ointment plus massage to the left ankle. One month after the child was first seen, the lesions showed signs of regression with the formation of more scar tissue and only slight deformity of the left ankle.

SUMMARY

A case of congenital ectodermal defect of the scalp is presented. The scalp lesion is typical clinically of the majority of cases previously described. However, the ankle lesion, unlike most ectodermal defects, is not symmetrical and is associated with a decided deformity due to scar tissue formation.

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American Academy of Pediatrics

Proceedings

FOURTEENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

BOOK-CADILLAC HOTEL, DETROIT, MICH.
JAN. 15-18, 1946

Report of the Secretary

The rate of increase in the number of Academy members continues and with it naturally an increase in work in the Secretary's office. The South American Division, Region V, has not been quite so active as it was previously, probably due to the action of the Executive Board at its last meeting to increase their dues.

Largely, the Academy has been interested in the proposed Federal Legislation and has voiced a very heavy majority objecting to many of the measures in the so-called Pepper bill. There is no feeling in the Academy that the objects which this bill seeks to attain are in any way opposed to the principles upon which the Academy has functioned since its beginning, but there is a feeling that the measures proposed for carrying out these objects are inimical not only to the profession but likewise to the objects themselves.

Another chief activity of the Secretary's office has been the reinstatement of the men coming out of service. These men come out on terminal leave and then are discharged, at the end of a certain length of time, from the service. We have regarded the final discharge as the termination of service and have adjusted our books to meet this situation. A member is booked for a year's exemption from dues, January first or July first, depending upon which date is closest to the completion of his terminal leave. Each of these men must pay \$5.00 for the JOURNAL since our contract with the C. V. Mosby Company demands this. There has been a great deal of difficulty in getting in contact with these men. Naturally, they do not think of writing to us immediately after they leave the service and sometimes their letters have been returned to us and we have had to bother other members of the Academy to obtain mailing addresses. Fortunately, we have received practically 100 per cent cooperation from these members and I wish to take this opportunity to thank them for their kindness.

The Post-War Planning Committee has been most active. Dr. John P. Hubbard of Boston has been made permanent Executive Officer for this Committee with offices in Washington. The Committee has had the active cooperation of both the Children's Bureau and the United States Public Health Service. They are getting things under way and a survey is almost completed in North Carolina, the first state where such survey has been made. A more detailed report will be given by the Chairman of the Committee, Dr. Warren R. Sisson.

Another major activity of the Academy has been the attempt to place men coming out of service in positions which they desire. Many want only refresher courses. This is true especially of the members of the Academy. However, the Academy has been able to obtain from Mead Johnson and Company a grant of \$10,000 for the next two years' work and a special secretary has been set up in the Secretary's office for carrying on this work, under his supervision. This work is just getting under way, but we hope to be able to do something which will be of value.

The Committee on Cooperation with the American Legion, with Dr. Hugh McCulloch as Chairman, has been most active and the Secretary has attended meetings where the group from the Academy and that from the American Legion developed plans for cooperation. This promises to be an activity of a great deal of value to veterans' families and, in general, to pediatrics in the United States.

Few of the members realize the difficulties of holding meetings under present conditions. Hotels are inclined to look somewhat askance at such meetings and are not overanxious to hold them since their rooms are filled with transient guests. In addition to this, transportation is peculiarly bad and all in all the difficulties are much greater than they were previous to the war. We may have to revise our ideas regarding hotels and meetings in the not distant future. There is even a possibility that the hotels will charge for space for holding meetings and for exhibits.

I cannot conclude this report without mentioning the exertions of the President in the behalf of the Academy. He has been most active in several projects and his presence in Washington has on many occasions and in many ways been a tower of strength to the Society.

It is now my unpleasant duty to report to you the names of those who have left us since the last meeting:

Dr. Phillip S. Astrowe, Kansas City, Mo.
 Dr. Edward S. Babcock, Jr., Sacramento, Calif.
 Dr. Jules M. Brady, St. Louis, Mo.
 Dr. Thomas B. Cooley, Detroit, Mich.
 Dr. Manning C. Field, Brooklyn, N. Y.
 Dr. Charles G. Kerley, New York, N. Y.
 Dr. Robert George McAliley, Atlanta, Ga.
 Dr. Frederick B. Miner, Flint, Mich.
 Dr. Archibald D. Smith, Garden City, N. Y.
 Dr. T. M. Watson, Greenville, N. C.
 Dr. Edwin B. Weldon, Bridgeport, Conn.
 Dr. James L. Winemiller, Great Neck, N. Y.

Respectfully submitted,
 CLIFFORD G. GRULEE,
 Secretary

Report of Region I

Arrangements have been made to hold the postponed meeting of Region I, on April 2, 3, and 4, 1946, at the Hotel Pennsylvania, New York City. Dr. Miner C. Hill, Chairman, and his committees are working diligently to make this one of the most outstanding meetings Region I has ever held. Members of the Academy from other regions are most cordially invited to attend.

The term of Associate Chairman, Dr. Louis Webb Hill, expires in 1945. Our constitution states, "The Associate Regional Chairman shall be appointed by the President of the Academy, after confirmation by the Executive Board, from a group of two or more candidates nominated by the State Chairmen of the Region." I have been instructed by the State Chairmen to present the names of Dr. Paul W. Beaven, Rochester, N. Y., and Dr. Warren R. Sisson, Boston, Mass., to the Executive Board for confirmation.

Shortly after Senate Bill 1318 was presented by Senator Pepper, I made arrangements for the bill to be sent to each State Chairman, except those in Canada. They were requested to study the bill, and in turn have as many Fellows as possible both read it and furnish to me their constructive opinions and criticisms. I have received replies from over one hundred Fellows. Less than 10 per cent were in favor of the bill. All were in favor of the objectives as expressed in the Academy's "Report of a Committee on a Consideration of Child Health

in the Postwar Period," JOURNAL OF PEDIATRICS, Volume 25, page 625. All of these letters have been sent to Dr. Grullee, our Secretary, so he can correlate the impression of the Academy's members throughout the country for the benefit of the Executive Board at its next meeting.

I wish to express my appreciation and thanks to the State Chairmen and Fellows of this region for their frank and cooperative spirit in offering these constructive criticisms. It is interesting to note that the majority of Fellows feel that health measures in Washington should be under the direction of the Public Health Department, and that the Children's Bureau should be transferred from the Labor Department to the Public Health Department.

Respectfully submitted,

OLIVER L. STRINGFIELD,
Regional Chairman

Report of Region II

Region II held a meeting of State Chairmen in Cincinnati on November 14, at the time of the Southern Medical Meeting. Those present were:

Dr. Wm. Willis Anderson, Georgia
Dr. W. W. Nicholson, Kentucky
Dr. Harvey Garrison, Mississippi
Dr. Carroll Pounders, Oklahoma
Dr. William Weston, Jr., South Carolina
Dr. James C. Overall, Tennessee
Dr. James B. Stone, Virginia
Dr. Russell C. Bond, West Virginia

Each State Chairman had about the same report to make, that is, that all the Pediatricians had been overworked and no organized Academy activity had been done.

There was considerable discussion of the EMIC program. Everyone expressed dissatisfaction with its practical working out. The men felt that the large amount of paper work far outweighed the small fees obtained. Dr. Overall had some interesting figures from the Tennessee Board of Health showing the comparative fees paid the obstetricians and pediatricians in that state. The obstetricians' fees were ten to fifteen times what the pediatricians get, mainly because of the excessive paper work required of the pediatricians.

These figures illustrate what the members said, that is, that the pediatricians were looking after the children for nothing as a patriotic duty and not sending in the claims for fees.

The fervent hope was expressed by all that EMIC would not become a permanent thing.

It was unanimously voted that the Pepper bill in its present form should not be passed by Congress. The State Chairmen had polled every member of the Academy in Region II and had found just three members who are in favor of the Pepper bill. All three of these men are full-time salaried men and not practicing pediatricians.

It was unanimously voted that if the Pepper bill should pass Congress there should be a means clause added for each state because the average income varies so much in different parts of the country. This would be especially true in the South where the average income is lower than in other states.

It was voted unanimously that before any action is taken on the Pepper bill that the Academy members be polled and the Executive Committee act according to the poll.

Respectfully submitted,

JAMES W. BRUCE,
Associate Regional Chairman
(Acting Chairman)

Report of Region III

Neither State Chairmen nor State Committee Chairmen were asked to submit reports of Academy activities within their respective states for inclusion in the Region's report to the January meeting of the Executive Board since it was felt that no abatement had, as yet, occurred in the heavy load being carried by civilian physicians. Hence, no state-by-state analysis of progress made will be attempted in this report as was the custom in prewar years.

However, interest in the revival of full Academy activities in the Region, now that the war is over, points up from several directions. First of all, plans are under way for a meeting of Region III in the spring of 1946. Earlier it was announced that the meeting place would be Chicago, but failure to secure suitable hotel facilities forced a change. According to present plans the meeting will be held at the Hotel Netherlands Plaza in Cincinnati on May 6, 7, and 8. It is hoped that by that time travel conditions will have improved and servicemen will have returned to civilian status so that a top-notch convention can be held with all hands present. In the meantime, several State Chairmen have informed the Regional Chairman that committee personnel is being reviewed preparatory to resuming activities abandoned during the war years. Attention to this phase of Academy work should be among the first to receive attention in all the states of the Region.

Applications for membership have continued on about the same level in spite of absence of many prospective members in military service. Eighteen applications were approved by the Executive Board at its June meeting and seventeen have been submitted for the Board's consideration in January. The total enrollment in Region III now numbers 469.

There have been no receipts or disbursements of funds of the Region since its last meeting. The present financial statement for Region III is as follows:

On deposit in savings account as of January 21, 1943	\$2,165.24
Interest to November 1, 1945	46.44
Total	\$2,211.68
Bonds held by the Treasurer of the Academy to the credit of Region III (Purchase value)	\$1,850.00
(Face value \$2,500.00)	
Total assets of Region III	\$4,061.68

In common with the other regions of the Academy, Region III looks forward with anticipation to the January meeting in Detroit, not only because it will be the first postwar convention of the National Academy, but because of the opportunity it affords for resuming scientific presentations, and, of especial importance at the moment, for the opportunity it provides for considering the pressing social and economic problems with which the practice of pediatrics is faced.

Since the January meeting of the Executive Board marks the termination of the Regional Chairman's terms of office, he wishes to take this opportunity of expressing his appreciation to the members and officials of Region III with whom he has worked so pleasantly during the last four years.

Respectfully submitted,
LEE FORREST HILL,
Regional Chairman

Report of Region IV

Region IV has held no annual meeting since the San Francisco meeting in May, 1941. It is hoped and contemplated that one may be held in the early summer of 1946. At this writing neither the time nor place of the meeting has been determined. Hotel accommodations in the coast cities are still overtaxed with military requirements, and it cannot at present be stated when this situation will be relieved. A canvass of the State Chairmen indicated the desire for a centrally located meeting in May, June, or July. If arrangements can be made, a meeting will be held in one of these months in or near San Francisco.

Report of the Treasurer

STATEMENT OF RECEIPTS AND DISBURSEMENTS

JULY 1, 1945, TO DECEMBER 31, 1945

balance in checking account, July 1, 1945	\$ 344.33
balance in savings account, State Bank & Trust Company	3,838.72
balance in savings account, First National Bank & Trust Company	1,544.01
	<u>\$ 5,727.66</u>

Receipts:			
Dues		\$26,705.75	
Wartime Assessment		6,445.00	
Exhibits, January, 1946, Meeting		7,965.00	
Annual meeting registration, January, 1946		1,834.00	
Annual meeting clinics, January, 1946		556.00	
Initiation fees		1,475.00	
Interest earned		487.12	
Pamphlets—Child Health Record	\$ 163.36		
Immunization Procedures	255.70		
Vitamins	15.90	434.96	
		<u>816.25</u>	
Subscriptions, Men in Service		10,000.00	
Committee, Post-War Courses		8,000.00	64,719.08
Committee, Post-War Planning			<u>\$70,446.74</u>

Disbursements:			
Annual Meeting, January, 1946		415.85	
Bank charge and exchange		94.22	
Certificates and mounting		38.52	
Executive Board		383.02	
Miscellaneous		265.22	
Office supplies and equipment		111.87	
Postage		199.14	
Rent		1,512.53	
Salaries—Secretary	\$3,750.00		
Assistant Secretary	450.00		
Stenographer	1,140.00		
Office	710.21	6,050.21	
		<u>161.33</u>	
Stationery and printing		7,620.16	
Subscriptions		226.79	
Telephone and telegrams		95.65	
Travel—Secretary		85.00	
Treasurers' bonds			
Expense—Region V	\$1,447.87		
States—Region I	19.73		
Region III	2.16		
Committees—			
Cooperation with American Legion	367.40		
Post-War Courses	240.86		
Post-War Planning	3,488.56	5,566.58	
		<u>9.98</u>	
Pamphlets—Child Health Record		21.42	
Immunization Procedures		.78	
Vitamins		32.18	22,858.27
Balance, Dec. 31, 1945			
Balance in checking account, December 31, 1945			\$47,588.47
Balance in savings account, State Bank & Trust Company			34,865.78
Balance in savings account, First National Bank & Trust Company			5,332.56
Balance in checking account, First National Bank & Trust Company			1,552.33
			<u>5,837.80</u>
			\$47,588.47

State Chairmen's Reports

Hawaii.—Dr. Donald C. Marshall reports little Academy activity. All but two members have been in the Armed Forces, and these two have been overwhelmed with work.

Oregon.—Dr. Carl G. Ashley reports the addition of eight new members out of nine eligibles. He also reports a unanimous opposition to the Pepper bill. Dr. Bridgeman has worked out an acceptable record card to be used for all summer camp inspections. Dr. Henricke has acted as liaison officer with the American Legion. Dr. J. W. Rosenfeld, after nineteen years of service, has submitted his resignation as Medical Director of the Visiting Nurse Infant Welfare Clinics.

The individual membership has attempted to cooperate with the EMIC program, but there have been numerous complaints of complicated record forms, delay in paying claims, and ridiculously low allowances for medical care in many cases.

Idaho.—Dr. Tremaine reports that one of the three members is still in the Navy.

St. Luke's Hospital in Boise is increasing its capacity one hundred beds, fifty of which will be occupied by an entirely new pediatric department.

The Crippled Children's Project is being decentralized with centers in northern and eastern Idaho as well as in Boise.

Dr. Tremaine also reports that Idaho has a greatly increased population and that there are several places either possessing good hospitals or projecting them, where pediatricians are urgently needed.

Utah.—Dr. Edwin R. Murphy reports that the membership has been extremely overloaded with work and that no time has been spent on Academy activity. The members have supported the EMIC program exceptionally well but view the Pepper bill with grave concern.

Arizona.—Three members are still in military service.

Dr. Vivian Tappan reports that efforts are being made to establish public schools for substandard children in Phoenix and Tucson. The purpose is to offer educational and vocational training for children handicapped by chronic noninfectious diseases (rheumatic fever, asthma, recurrent nontuberculous pulmonary diseases, bronchiectasis, etc.) and for mentally retarded children for whom no provision exists. In Tucson, beginning in September, 1945, special classes for substandard children were opened in each of two schools.

During the past year two hospitals in Arizona have built specially equipped modern nurseries for the care of the newborn.

The Arizona Pediatric Society has supported the EMIC program, examined children admitted to the Crippled Children's Service, and until the past year supervised the Nursing Conferences.

California.—Cochairmen Drs. Crawford Bost and Ezra Fish report that pediatric activities have been reduced to a minimum due to the stress of practice.

The Academy cooperated with the Los Angeles Heart Association in a three-day symposium on rheumatic heart disease.

Washington.—It is with regret that we report that Region IV suffered a great loss in the death of Dr. E. J. Barnett, of Spokane.

With the war over and with some of our members already home and others due in the not too distant future, we look forward to a less arduous life and to more time to spend on Academy problems.

Respectfully submitted,

HUGH K. BERKLEY,

Regional Chairman

Standing Committees With State Activities

Report of the Committee on Cooperation With the American Legion

During the interval since the last report from this Committee to the Executive Board, there has been a meeting of the Committee in Chicago on Oct. 6, 1945. The meeting was attended by all members, and by Dr. Grulee; and by Mr. Harry C. Kehm, Chairman of the National Executive Committee of the Child Welfare Division of the American Legion; Miss Emma C. Puschner, Director; and Mrs. Marguerite G. Seibert, Assistant Director of the Division. It was the first meeting of the whole Committee, and considerable time was used for discussion of general principles for cooperation with the Legion and the part the Academy might undertake in the development of the Legion plan for child welfare. Mr. Kehm spoke fully of what the Legion is doing in this field, and of the opportunity and need for cooperation with the Academy.

Dr. Edward C. Mitchell has arranged for the publication of short articles on various subjects in the field of child care and welfare in the *National Legionnaire*, the monthly news sheet of the Legion. Arrangements are being made for the preparation of these articles by members of the Academy and other pediatricians selected for the subject. It is proposed that these articles be published monthly so long as they hold reading interest. About 2,000,000 copies of this publication are sent out each month. An article on rheumatic fever was prepared by Dr. George M. Wheatley at the request of the Legion and was published in the October number of the *American Legion Magazine*.

There was a discussion of plans for Academy participation in the Legion "April—Child Welfare Month" plan. Region and State Liaison Officers of the Academy will be requested by Legion representatives locally as the need arises.

Dr. Richdorf was selected as a member of the Committee who should show to members of the Academy who are Legionnaires, and, especially to members of the Academy who are being separated from military service, what the Legion is doing in the field of child welfare. It is recommended by the Committee that this group of professional pediatricians be used wherever possible to develop interest in the Legion Child Welfare Program, and should be selected as state liaison officers with the Legion.

Respectfully submitted,

HUGH McCULLOCH, Chairman

Edward C. Mitchell, Honorary Chairman

L. F. Richdorf, Associate Chairman

E. T. Wyman, Region A Liaison Officer

P. A. McLendon, Region A Liaison Officer

G. M. Lyon, Region B Liaison Officer

J. H. Hess, Region C Liaison Officer

Clifford Sweet, Region D Liaison Officer

Report of the Committee on Cooperation With Nonmedical Groups

The chief accomplishment of this Committee during the past year was the preparation and distribution of a Health Card for use in camps and summer schools. A large number of these cards were ordered by the National Girl Scouts organization and several other camping groups. Numerous favorable reports have been received from camp physicians.

Various child organizations are now being contacted to determine ways in which the Academy can assist them in their health program.

Respectfully submitted,

ALBERT D. KAISER, Chairman

Roger L. J. Kennedy

Marvin Israel

Joseph I. Linde

Margaret Nicholson

James C. Overall

Warren R. Sisson

Lillian R. Smith

Edwin T. Wyman

Report of the Committee on Governmental and Medical Agencies

This Committee has held no meeting since May. The May report showed the full completion of both State and National programs of cooperation between Governmental and Medical Agencies approved by the Executive Board in June.

Respectfully submitted,
 STANLEY H. NICHOLS, Chairman
 Paul W. Beaven
 W. L. Crawford
 Alexander T. Martin
 Oscar Reiss
 A. L. Van Horn

Standing Committees

Report of the Committee on Fetus and Newborn

I. Question of Dr. D. Lesesne Smith:

Change of State laws in regard to eye prophylaxis with a view to the use of penicillin in place of silver nitrate.

Answer:

The Committee members hold the opinion that it is not advisable to recommend any change in laws or regulations relating to the use of silver nitrate for prophylaxis of the newborn infant's eyes because evidence in regard to the efficacy of penicillin in eye prophylaxis is inadequate.

II. Question of Dr. Jerome Glaser:

Definition of the newborn period.

Answer:

The Committee recommends:

1. That the term "neonatal" rather than "newborn" be used to cover the period after birth that Dr. Glaser asks us to define.
2. That, for the sake of uniformity, the first month (first 30 days) should limit the neonatal period. This may be regarded as an official definition since it has been agreed upon by the Children's Bureau, the American Public Health Association, and the Bureau of the Census (the Registrar, Bureau of the Census, U. S. Department of Commerce, Vol. 4, No. 2, February 15, 1939).

Respectfully submitted,
 ETHEL C. DUNHAM, Chairman
 Nina A. Anderson
 John C. Montgomery
 Howard J. Morrison
 Milton J. E. Senn
 Charles A. Weymuller

Report of the Committee on Legislation

Report to be given personally by Chairman at the meeting.

Respectfully submitted,
 JOSEPH S. WALL, Chairman
 Jay I. Durand
 Harvey F. Garrison
 Philip Van Ingen
 Alfred A. Walker

Report of the Committee on Pan-American Scholarships

We have now eleven scholars; the last of these will have completed his course on Oct. 1, 1946. No arrangements are being made for new scholars for the next two years, owing to the crowded condition of our clinics as a result of men coming home from service.

Respectfully submitted,

CLIFFORD G. GRULEE, Secretary

Report of the Committee on Pediatric Awards

The Committee recommends that, for this year, the Mead Johnson Awards should not be made. It appears that it is better to do this than to lower the standard required for the awards which, in the past, have been given for work of outstanding merit. The Borden Award will be presented.

Respectfully submitted,

S. GRAHAM ROSS, Chairman

Oscar M. Schloss

Joseph Stokes, Jr.

Wilburt C. Davison

Grover F. Powers

Report of the Program Committee

The Program Committee recommends that a Full Program consisting of Round Table Discussions, Panels, Symposia, and individual speakers be arranged for the next Annual Meeting of the Academy.

Respectfully submitted,

EDGAR E. MARTMER, Chairman

Frank H. Douglass

R. Cannon Eley

M. Hines Roberts

Matthew Winters

Special Committees

Report of the Committee on Geographical Distribution of Pediatricians

To date I have completed about twenty-eight separate surveys and have covered more than one-half of the requests as per the list sent to me by Dr. Grulee. Some of the surveys were rather lengthy and covered much territory. Each survey included (1) the population and increase or decrease of same for past five years; (2) the total number of physicians, plus increase or decrease; (3) the total number of Pd*, Pd, FAAP, and Diplomates (1937-1942); (4) university and hospital facilities for a given locality, city, county, or state. This gives the sort of information that is helpful in estimating the growth of a locality within the five-year period from 1937 to 1942.

I have had letters from several men who have indicated that the survey has been helpful. The remainder on my list will be finished soon.

Respectfully submitted,

OTTO L. GOEHLE, Chairman

Report of the Committee on Rheumatic Fever

Our Committee has not met as a group since the meeting in St. Louis one year ago, but has conferred individually and by letter so that the work of the Committee has been kept activated. The Committee notes with satisfaction the publication in a separate booklet the entire Symposium on Rheumatic Fever held at the St. Louis meeting. This has been done by the Pennsylvania State Department of Health and has been distributed throughout the State for educational and promotion purposes. The American Council on Rheumatic Fever has been set up and incorporated under the leadership of the American Heart Association. Two mem-

bers of the Committee are represented on this Council, which is also represented by other organizations such as the American Medical Association, American College of Physicians, American Public Health Association, American Rheumatism Association, American Hospital Association, American Nurses Association, and American Association of Medical Social Workers.

The Committee has three broad objectives:

1. Educative
2. Standard-setting
3. Evaluation

The educative function of the Committee was focalized in the Symposium on Rheumatic Fever at the St. Louis Session in 1944. The Standard-setting function will be the concern of the Committee at the Detroit session, and a joint meeting with the School Health Committee will be held to discuss standards for diagnosis and the principle of a cardiac consultation service for school children. The evaluation of results of the various state programs is an important objective and it is hoped that this may be worked out in cooperation with the Children's Bureau.

A recent communication has been received from a group in Montevideo with a specific mention of the role which the Academy has taken in the field of rheumatic fever. The high incidence of rheumatic fever in the Armed Forces in both World Wars has augmented the public interest in this disease. This, in turn, is a challenge to the Academy to contribute its resources in the control of a disease which is essentially a disease of childhood.

Respectfully submitted,

ALEXANDER T. MARTIN, Chairman

Stanley Gibson

John P. Hubbard

Hugh McCulloch

Eugene H. Smith

R. R. Struthers

George M. Wheatley

Report of the Committee on Post-War Courses in Pediatrics

The immediate objectives of this Committee were (1) to ascertain approximately how many medical officers returning from military duty after the war would wish to take post-graduate courses and other types of training in the field of pediatrics, and (2) to survey the pediatric training facilities of the United States and Canada in order to determine to what extent such demand can be met. The ultimate aim of the Executive Board of the Academy was to develop, on the basis of the Committee's findings, an effective mechanism for aiding our deserving medical veterans to find suitable opportunities for further training in their chosen field.

The first immediate objective was attained by the Committee's being given free access to the returns from Dr. Grulee's poll of Academy members serving with the Armed Forces and to the results of a large-scale, systematic survey carried out among Medical officers by Lieutenant Colonel H. C. Lueth. Approximately 30 per cent of the Academy members in the various services expressed a desire to take from one to four months of informal postgraduate training in a pediatric clinic or hospital before returning to office practice. A still larger number have subsequently expressed a wish for short, intensive, more or less didactic refresher courses in pediatrics and related fields. A small number of those members who have written to the Committee have manifested an interest in obtaining full-time academic or hospital positions with more or less permanent tenure.

On the basis of Colonel Lueth's questionnaire returns from 21,029 officers it was estimated that a total of between 2,200 and 2,400 physicians serving with the Army, Navy, Public Health Service, and Veteran's Administration would wish to have further training in pediatrics following their release from duty. One-third of these, mostly the older men, expressed a need for short courses only, while the others wanted from one to three additional years of training.

Fifty per cent of the older officers and 80 per cent of the younger men expressed a desire to prepare for certification by the American Board of Pediatrics. It was impossible to obtain reliable information in advance regarding the rate at which such medical officers would be released from duty.

Returns from the various polls indicate that the following types of training opportunities are needed: (1) Informal postgraduate "brush-up" experience of several months' duration in a general pediatric clinic. About 120 veterans who are members of the Academy desire such an opportunity. (2) Intensive, more or less academic, refresher courses of a few days to a week's duration for several hundred previously well-trained pediatricians who have not been able to keep up to date with the newest developments in the field. (3) Straight or full-time internships in approved pediatric hospitals and outpatient clinics for young physicians wishing to specialize in pediatrics but who were trained in other branches of medicine or had rotating internships only before entering the service. (4) Assistant residencies in pediatrics for physicians who had but one full year of clinical training in the field before being inducted into the Army or Navy. (5) Residency positions for those men who had previously served both internships and assistant residencies. (6) Teaching assistantships and research fellowships for those veteran pediatricians, who have completed the two years of special training required for certification by the American Board of Pediatrics but who need or desire to attain still greater competence in their field before turning to practice or seeking an academic or other regular position.

To accomplish its second preliminary objective the Committee prepared a comprehensive (but simple-to-answer) questionnaire, mimeographed copies of which were sent to the professors of pediatrics or chiefs of service in 77 leading medical schools and hospitals in Canada and the United States. Questionnaires were completely filled out and returned by 61 representative institutions. This was regarded as a good return, considering the current demands on the time of such administrators.

Analysis of these questionnaire returns indicates that 80 per cent (the percentage replying) of the 77 pediatric clinics polled, list the following total numbers of regular full-time training positions in pediatrics without regard to wartime quotas: 134 straight internships, 173 assistant residencies, 93 residencies, 63 research fellowships and 58 teaching assistantships, totaling 687 training positions. On this basis there should be a total of about 860 positions in the 77 institutions. In addition, the 61 institutions listed a total of 166 rotating internships. The total numbers of additional full-time training positions of standard quality which these 61 institutions said they could create without committing themselves for maintenance or financial stipend were as follows: 89 straight internships, 116 assistant residencies, 81 residencies, 86 research fellowships and 91 teaching assistantships, totaling 463 potential training positions. This would indicate approximately 580 potential new training positions in the 77 institutions. It is obvious from inspection of the returns, which showed in addition to the foregoing data, such information as bed capacity, outpatient clinic attendance, etc., that many more than this number of new training positions could be made available, if even minimal financial support for the trainees could be provided. It is recognized that support from the G. I. Bill and personal savings of veterans, set aside for such purpose, may make many of these potential positions acceptable, if the demand for training opportunities far exceeds the supply.

Under ordinary conditions a large percentage of the 860 regular full-time training positions referred to above as occurring in 77 institutions and others not listed are filled by civilian physicians coming up through the ranks. However, the new order recently issued by the Army and Navy for induction into service of all reserve officers in positions beyond the internship level after April 1, 1946, will release all assistant residency and residency positions other than those held by women and men on 4-F status. These vacancies and all of the new or potential positions already referred to should be available to medical veterans desiring them.

There are many additional public, private, and semiprivate clinics for children which could offer suitable training positions if they were affiliated for the purpose with the larger pediatric teaching clinics. In some of the larger centers, local committees have made plans

for creating suitable rotations between various types of service in such nonteaching hospitals and regular teaching hospitals for the purpose of increasing the number of acceptable positions available. It is hoped that many other such arrangements will be organized.

The Committee had sincerely hoped to accumulate sufficient information regarding available training positions and postgraduate courses throughout the United States and Canada to permit their being catalogued for immediate service to our medical veterans upon their return to civilian status. However, the suddenness of the war's termination, which had not been anticipated, and the unavoidable delays incident to the necessity of conducting most of the work of the Committee by correspondence, found the organization unprepared to give substantial help to the first contingent of returning medical officers. While the Chairman of the Committee has been able to assist a fair number of physicians to find suitable training positions by correspondence, lack of a list of vacant positions and of spare time for correspondence has made it impossible for him to reply to all inquiries.

At the only meeting held by the Committee, that in Galveston, Texas, on November 16 and 17, it was agreed to recommend to the Executive Board of the Academy that a central clearinghouse for training positions be set up in the Office of the Secretary in Evanston, Ill., to handle all correspondence pertaining to training positions for medical veterans. The recommendation included the proposal that a grant of money be requested from some outside agency known to be friendly to the purposes of pediatric education and practice to defray the costs incident to this prodigious new undertaking for a period of at least two years. Dr. Grullee, who attended the meeting at the request of the Committee, agreed to approach the Mead Johnson and Company or the Kellogg Foundation for a grant of \$5,000 per year for a period of two years. In response to a letter from Dr. Grullee, the Mead Johnson and Company generously contributed the sum requested, which insures the carrying out of the Academy's new service to its own members and to other medical veterans wishing to specialize in pediatrics.

In order to expedite the work of the central office, an explanatory form letter has been sent by the Committee to the 77 institutions which received the original questionnaire with the request that they supply the Academy Office with complete and up-to-date lists of all service-connected physicians and veterans applying for positions and courses in pediatrics and also lists of training positions, both regular and specially created, which are expected to be vacant. Much duplication of correspondence will be avoided by this means.

Those receiving the letter will be asked if they cannot invite at least two veterans Academy members at a time to spend a period of three months each as informal guests of their clinics. During this time such pediatrically trained veterans would undoubtedly be able to get back into the swing of clinical practice in their field. It was the consensus of the Committee that this kind of opportunity would satisfy the needs of most Academy members and other pediatricians with similar training and aspirations. Since a fair-sized number of returning Academy members have manifested special interest in short intensive refresher courses, those institutions offering such opportunities are requested to furnish notices of the same. These will be classified according to type of course offered and geographical location for use by the central office in replying to inquiries received.

Judging from the questionnaire returns, the Committee members are convinced that this clearinghouse service for bringing available candidates and surplus positions together will prove to be so useful that numerous requests will come to the Academy for its continuation beyond the period of the present emergency.

Respectfully submitted,

IRVINE MCQUARRIE, Chairman

Harold K. Faber

Stanley Gibson

Alton Goldbloom

Arild E. Hansen

Joseph A. Johnston

Rustin McIntosh

Report of the Committee on Post-War Planning

Since the last report to the Executive Committee, the full committee on the Study of Child-Health Services, together with Mr. Rollo Britten of the U. S. Public Health Service, Mrs. Elizabeth E. Boles of the Hospital Commission, Drs. Katherine Bain, Charles L. Williams, Jr., and Joseph Lachman, met in Chicago on Oct. 20, 1945.

The most important development since our October meeting has been Dr. John P. Hubbard's acceptance as Director of the Study. Dr. Hubbard is a member of the Academy, was in active practice before the war, and has more recently been a Colonel with the A. M. G. with assignment in Denmark. We are fortunate to have as our Director a physician with keen clinical interest and appreciation of medical needs and experience in medical organization. As you will recall, our technical staff now consists of Dr. Hubbard as Director with Dr. Bain and Dr. Williams as associates. I have asked Dr. Hubbard to be present at the Executive Committee meeting to give you first-hand his impressions of the Study up to date and to outline future plans.

The pilot study in North Carolina was started in October under the supervision of Dr. Joseph Lachman. We are at this time very much gratified by the unequivocal cooperation between the Academy members and our study group. The study has progressed very satisfactorily and will be concluded this month. An exhibit of the methods employed in this pilot study will be presented at the Detroit meeting.

One of the most pressing needs is more adequate office space. We are now ensconced at our headquarters in Washington at the Children's Hospital with a half-time secretary. This is most inadequate and we need room not only for the technical staff with increased secretarial assistance, but also space for the increasing volume of correspondence and completed schedules. We have been able to locate possible suitable offices in Washington and this will be put before our advisory committee before final decision is made. You probably will recall that a space at the Children's Hospital, so kindly donated by that institution, consists of one small room, and further space is not available there.

One of the imminent problems concerns the financing of our Study. On Dec. 10, 1945, Dr. Hubbard, Dr. Bain, Dr. Dean Clark (formerly of the U. S. Public Health Service), and your Chairman had a conference with Dr. Van Riper, the Assistant to Dr. Gudakunst, who is Medical Director of the National Foundation for Infantile Paralysis. We feel justified in stating that a substantial sum will be assigned to us from the Foundation. On December 19, we meet again with the Rockefeller Foundation which we hope will be interested in aiding us in the educational study which is now about to be launched under the direction of Dr. James L. Wilson. We have also recently visited the Marshall Field Foundation in New York. We were very cordially received and have made a definite request for \$10,000 from them. We have taken under advisement the suggestion to request financial aid from pharmaceutical houses and manufacturers of baby foods, etc. It is hoped that in this way we will be able to obtain a number of grants of \$5,000 to \$10,000 each. We should like the advice and support of the Executive Committee in this matter.

The Committee also feels that the Academy of Pediatrics should consider renewing an allocation of \$8,000 to \$10,000 to the Study for another year.

Respectfully submitted,

WARREN R. SISSON, Chairman

John P. Hubbard, Director

Allan M. Butler

Harvey F. Garrison

Henry F. Helmholtz

Lee Forrest Hill

Joseph I. Linde

Borden S. Veeder

Joseph S. Wall

James L. Wilson

Report of the Committee on Tumor Registry

Report to be given at the meeting.

Respectfully submitted,

HAROLD W. DARGEON, Chairman

Hayes Martin

Herbert F. Jackson

Report of the Nominating Committee

Recommendations:

For Vice-President (President-elect)

Dr. Lee Forrest Hill

Des Moines, Iowa

For Chairman of Region III

Dr. George F. Munns

Winnetka, Illinois

Respectfully submitted,

J. A. HENSKE, Chairman

Hugh Chaplin

Hughes Kennedy, Jr.

Oscar Reiss

There are no reports from the following:

Committee on Contact Infections

Committee on School Health

Committee on Honorary Fellows

Committee on Hospitals and Dispensaries

Committee on Immunization and Therapeutic Procedures for Acute Infectious Diseases

Committee on Medical Education

Committee on Mental Health

Committee on Nursing Education

Committee on a Library and Museum of Pediatrics

Committee on Mothers' Milk Bureaus

Committee on National Defense

Committee on Nutrition

American Board of Pediatrics

The Social Aspects of Medicine

MEDICAL EDUCATION

PROPOSAL FOR DECENTRALIZED MEDICAL TEACHING AS AN AID IN IMPROVING MEDICAL CARE

It seems to be the consensus of all that, since a large part of the lower income groups of our population cannot get adequate medical care under our present system, tax money will and should be furnished in increasing amounts to provide them with it. The public is so thoroughly convinced of this that schemes to support medical care have become so politically profitable that numerous bills for such projects have been before Congress. All the proposed schemes, whether narrow in scope or so far-flung as to cover medical care for all at a cost of billions, practically ignore the problem of medical education or offer casual and nonspecific gestures of support. It seems obvious that no amount of money can give all our people good medical care except as medical schools supply us with more men with better education and training than at present. The techniques of medical education need radical revision from the first year up, but the most neglected period is in the early postgraduate years where, in the last decades, most of the clinical training is given. I believe that since the education of young physicians and the medical care of the poor has been in the past so advantageously associated to their mutual benefit, that energetic steps should be taken to encourage the extension of our medical education system to small cities and towns and even to rural centers and not restrict it, as at present, to a few great medical centers. It is obvious that no single plan will furnish a complete and good solution to the problem of the adequate distribution of good medical care, but we have almost entirely neglected fruitful opportunities already at hand.

In brief, I believe we should undertake a great expansion with improved organization of the present system of internships and residencies so that after the first three years of medical school, from three to six years of further clinical training be provided for each student who intends actually to practice medicine. The young doctor and his work should continue to be supervised by a medical school while he should be paid on an increasing salary schedule sufficient to allow him to live a normal life and assume family obligations. The clinical teaching for these three to six years should be in greatly increased numbers of teaching hospitals or clinics making use of a far larger clinical teaching staff, the members of which should themselves be continually under medical school influence. To implement this in part, the large teaching hospitals now connected with medical schools should have organized around themselves dependent satellite institutions from which medical and nursing home care will stem and to which the advantages of the teaching center with laboratory and clinical consultation and a supervised resident staff will be systematically extended.

The justification for such a program rests on the following beliefs:

1. Most physicians, like other men, need a constant urge to exert their best and few can drive themselves with only their conscience. Some stimulus of desire for large possessions, competition, pride, love of learning, fear of loss of income or prestige, exposure of work to criticisms, is necessary for energetic application to work and self-improvement, and the direction of development will be determined to a great extent by which stimulus is dominant.

A salaried physician with a future secured by government appointment often has little stimulus since no supervisory system organized and executed by a government agency can detect poor medicine except that of the gravest nature, or can exert any control of the quality

of medicine practiced except by regulations which will level all practice and handicap the best. Sound and fair criticism of a physician's work is exceedingly difficult except by another physician closely working with him.

Competition for patients does not result in good medicine. It is quite impossible for most lay people to judge a good physician or to distinguish good from bad treatment. A good bedside manner, an attitude of uncritical self-confidence, a ready treatment, good or bad, but positively offered for every complaint, often makes the most financially successful practitioner. The worst quack may have a great advantage over an excellent and honest physician.

2. Excellent medicine is likely to be practiced around a good medical school where the stimulus of teaching or learning is present, where diagnostic and therapeutic skill is under the constant observation of critical students and where records are kept for future analysis by others than he who makes them.

The danger of a cold inhuman "research" attitude around such teaching centers is real, though often exaggerated. Certainly, an attitude where "experimental" medicine in its bad sense is emphasized is frightening to patients and wrong under any circumstances. Ignorant and poor patients who permit such occasional abuses, more common by far in Europe, make very poor "material" for teaching students in any case. A student, from the beginning, should be in contact with patients who are demanding.

A medical school should play an active, vital and stimulating part in all the health activities of the community and state. Its activities should not be limited to academic teaching and research, or simply to turning out of finished doctors at the end of four years to go their own way. As medical education should continue during the lifetime of a physician, so a medical school should continue to play as active a part as possible in the practice of medicine of all physicians. The best student of medicine is a teacher. The best teacher is a student. The best practitioner is a constant teacher and student.

Although a good clinical faculty must include a number of full-time workers, a great deal of the teaching must and should be done by practitioners giving part time to the medical school. With proper organization and with good men, there is hardly a practical limit to the number of part-time teachers that can be of value.

Ideal instruction for students of clinical medicine, whether undergraduate or graduate, is by apprenticeship to a good and active clinician who is willing and able to teach and who can constantly stimulate the student to work in library and laboratory in frequent contact with organized research work. The assistance of a student of medicine to a practitioner of good ability, who allows free questions and discussion, stimulates him to his best efforts.

3. Medical education at present is considered by many too long and too expensive. Even so, a laudable tendency exists now in the best medical centers to increase the time spent in training by three to five years' residency in a hospital. This long training period is not unusual for the best trained doctors and is highly desirable for the good of the public; yet the young physician may thus not be self-supporting until after he is 30 years old, although he should be financially independent and able to assume the normal financial responsibilities of an adult far sooner. Many men, often the most intellectually able to profit by long training under supervision, must curtail their program of study because of financial pressure. In a long postgraduate education the resident physician performs an important public service by his work. In so far as he further trains himself, his contribution to the public good and his future patients becomes greater. It seems highly desirable that this extensive system of training should be encouraged and be paid for, and that many more opportunities for such training be provided. The need for resident physicians in our smaller hospitals is becoming more and more realized although the shortage of good positions forces many men to accept positions that are poorly organized for teaching. In fact, in the majority of internships, the young doctor is exploited by the hospital and made to work at preponderantly uninteresting routines for a little pay and a slipshod training. There is a great need to improve and increase the opportunities for hospital training.

There is a tremendous need in all but the largest teaching hospitals for more and better resident physicians and for resources to pay them.

4. Considerable state and private philanthropic effort has been directed to so-called postgraduate instruction, that is, attempts to bring physicians already some years in practice back to medical schools and hospitals for review studies and to be brought "up to date." Such instruction is often disappointing, the physician being too long away from his basic medical study to profit except from simple directions as to some latest therapy and the period that he can spend in "refresher" courses is short and intermittent. Attempts to re-educate a man, after he has been allowed to get out of touch with medical progress and forgotten the basic principles of physiology and pathology by which new information must be intelligently appraised, is obviously a poor substitute for a continued stimulus of medical study and training. The man is likely to be in a hurry to get back to his practice; the course is concentrated; at the time, he does not see the relationship between the theory taught him and his practice; the laboratory procedures recommended and techniques outlined often seem to be so beyond his skill that he quickly considers much that is taught too theoretical and impractical and rejects it. It would be much better to bring the consultant and teacher, with ability and willingness to contribute technical aid, to the practitioner in his own hospital and community while he is working on his own patients.

5. In the past, much of our clinical teaching has been in large clinics for the poor and has been supported by the charity of physicians who contributed their services and by others who furnished money. It certainly is the purpose of every statesman and every public-minded individual to wipe out the medically indigent and, since it is obvious that medical education must be continued at all costs, the "material" for clinical medical instruction in the future must come increasingly from the people for whom medical care can be paid. This tendency to use private patients for teaching should improve medical pedagogy and should be encouraged.

It seems obvious that if the systems of medical education be extended to make use of small hospitals for long residencies properly supported by suitable salaries, that the small hospital would benefit as well as the student who might not otherwise be able financially to take further training. Such an internship or residency, however, would not be justifiable unless the quality of instruction of the University center be maintained and extended to the small hospital. This, however, is quite possible. An interlocking system of satellite hospitals would need to be developed around each suitable medical school so that the satellite hospital can be a medical center for a small community and yet depend on the larger institution, possibly a considerable distance away, for special laboratory and x-ray services, for pathology and special consultants and a resident medical staff. The smaller institution with a good intern and resident staff, with paid local teaching physicians as they are available, supplemented by visiting instructors from the medical school, could, with the advantages of the laboratory and consultation service of a medical school connection, be kept as good a teaching organization for the graduate as the University hospital itself.

The local physicians who, in the course of years would ultimately be drawn from the group of residents, would be made teachers when their abilities allowed it, would have a constant opportunity for their own continued education, and frequent contact with the medical school teachers who, being responsible for the type of training of the residents and interns, would make frequent visits. All hospitals used for such a program should be the locus of doctors' offices with more efficient organization of secretaries and nurses and laboratory services than can be supplied by the individual physician. Our present "Out-patient Department" or clinic for the poor would disappear, as it should, and these patients be cared for in such a medical school sponsored collection of group practicing offices in hospitals.

The general plan of a complete medical education in such an organization would be based on four periods:

A. Premedical school. Still in the colleges with greater emphasis on basic sciences, psychology and sociology, three or four years.

B. Medical school, three years. Basic medical sciences with instruction in clinical techniques and study of disease, quite reorganized from what we have at present. The early courses in anatomy and morphological pathology should be shortened greatly to be retaught in the third year, after the student has become acquainted with the technique of approach to patients and has studied the symptomatology of disease. Physiology and bacteriology and chemistry would also be reviewed in the third year in connection with clinical problems.

C. Applied clinical medicine, two years. This should be a greatly improved rotating internship, full of supervised clinical responsibility but also with laboratory work in bacteriology and pathology. Much of these years would be spent in the larger hospitals although short periods, especially for supervised home visit experience, could be spent in the smaller and sometimes rural institutions.

D. An indefinite period of supervised medical practice lasting from two to five or more years, covering the work now done by residents, research fellows, junior teachers. These men, themselves under supervision, would do a large part of the intern instruction. They would enter their specialties, plan an academic life or pursue a training for general practice, not now available, during this period. The students under C and D should be paid a salary sufficient for a dignified living with family responsibilities.

No mention has as yet been made of the important problem of financing such a project. Inevitably the problem of the support of medical education and the whole controversial subject of the best methods of distributing medical care to the lower income groups are involved and no attempt here is made to solve these problems. No great increase in the medical care of our people or improvement in its quality can take place without far greater support of medical education. Great foundations, and State and National government agencies are full of plans for the support of specific research projects and for direct payment for medical care while allowing the basic budgets of medical schools to remain ridiculously inadequate, eked out by small grants begged for by men better engaged in professional activity. Medical schools should be given direct aid from tax money. It seems obvious that whatever is accomplished to extend better medical care to the lowest income group, money from public funds derived from taxation must be used. Inevitably, if tax money is used, the efficiencies of some sort of group practice will be necessary to reduce the cost. There seems no good reason why a medical school itself, with its own teaching staff expanded as described, should not organize a group practice system as a basis for teaching as well as giving good medical care. Whatever the future holds for us, whether tax supported medical program, private prepayment insurance programs, or a continuation of our present medical practice habits, the decentralized combined educational-medical care program outlined so briefly here could be carried out, and none of a variety of methods for financing it would seriously influence the usefulness of the basic idea of the program.

(Signed) JAMES L. WILSON

Ann Arbor, Michigan

It is no accident that the first medical journal in this country to launch a section on the social aspects of medicine as a regular feature happens to be the JOURNAL OF PEDIATRICS, a periodical by and for pediatricists. The very nature of their specialty has made them pioneers in the practice of preventive medicine. It is true that early pediatricists conceived their role of service in this field to be primarily the prevention of disease. This negative concept has recently enlarged to encompass the promotion and preservation of child health. Acceptance of this expanded sphere of service calls for as keen a knowledge of social conditions as of medical science itself. The medical forum inaugurated by the JOURNAL OF PEDIATRICS is a harbinger of the growing recognition by pediatricists of their expanding obligations as purveyors of medical care.

If the goal of child health promotion is the development of the whole personality of the child and the attainment in full of his inherent potentialities, social factors take on an importance equal to purely medical ones. The pediatricist has been at fault in his lack of interest and, because of poor educational preparation, in his inadequacy in this field of service. He has usually neglected such important social factors as housing, recreational facilities, and educational opportunities; has given too little attention to mental development, emotional adjustment, habit formation, and social fitness; and has in the main been satisfied to confine his efforts to dietary supervision, physical care, and specific prophylaxis against disease. In his capacity as a promoter of health as well as an arbiter of the sick, the pediatricist (and for that matter all physicians) should be willing and able to assume the task of initiating, guiding, and participating in individual and community health programs and of cooperating with all interrelated civic agencies interested in child welfare.

The traditional reluctance of the pediatricist (and physician) to recognize and accept his heightened social responsibilities stems directly from his educational background as a medical student and hospital house officer. His undergraduate medical curriculum in the clinical years was focused on the study of pathology and disease; in his hospital training, the chief focus remained the diagnosis and treatment of the sick. Throughout his formal training, the preservation of health *per se* and its dependence on social factors were minimized and instruction often relegated entirely to the Department of Public Health with perhaps additional smatterings gleaned from enlightened Departments of Pediatrics and Medicine. It is precisely in this sphere of medical practice that I believe medical education has been found wanting.

Has not the time arrived to give consideration to a revision and reorientation of medical education, general and pediatric, at both undergraduate and graduate levels, to keep abreast with the enlarging sphere of medical practice and the expanding duties of physicians? The spirit of *laissez faire* which marked the last century is rapidly crystallizing into one of social consciousness and the doctor must be properly trained to keep step with changing trends if he is to retain civic leadership in medical matters.

This column is not the place to present in detail revised medical programs of pediatric education designed to stress health promotion. They will necessarily vary in different institutions and localities and their experimental nature will subject them to further revisions with added experience. To start discussion, it will suffice to mention here a number of hitherto relatively neglected instructional mediums which might be put to more effective use. Of first importance is the home and family set-up. Every trainee should be given the opportunity of making home visits and furnishing domiciliary medical care under adequate teaching supervision. Other potentially valuable mediums include prenatal clinics, newborn nurseries, pediatric outpatient departments with opportunities for working in well-baby, adolescent, prophylactic, and mental hygiene clinics, baby health stations, schools (nursery through secondary), recreation centers, juvenile courts, adoption bureaus, foster homes, and convalescent institutions. Attendance, observation and preferably participation in the activities of all or some of these agencies under supervision would serve to acquaint the trainee with the manifold number and variety of interested agencies and the precise contribution of each to the common goal of child health and welfare.

Instruction of this kind would enable the prospective pediatricist in the course of his training to work in close collaboration with public health nurses, social workers, nutritionists, public health officers, psychologists, teachers, and above all parents and siblings in the home environment. In later practice, he would not be at a loss as he so often is now without previous experience when he seeks help from civic groups for his patients. Maximal progress in child health promotion can only accrue from the joint efforts of all groups, lay and professional, voluntary and official, and the well-trained pediatricist would possess the knowledge and background to make a real contribution.

The objection may be raised, not without justification, that pre-eminence in medical education in the United States has been reached through the concentration of resources in a limited number of basically important fields and that any attempt to enlarge the already

heavy burden imposed on medical students and hospital house officers will lead to confusion and turmoil. This policy of subordinating expansion to excellence is in general a wise one, but the enlarging role of the physician in society urgently calls for reevaluation of the aims of medical education. If time limitations require reasonable reduction in the hours assigned to traditional clinic lectures, bedside teaching and impatient rounds, the benefit derived is, I believe, worth the sacrifice.

The purpose of this section is to invite discussion on medical questions of a social nature. The interrelated questions of pediatric (medical) education and the heightened social responsibilities of the pediatric (medical) practitioner have been posed in the hope that frank discussion will stimulate interest and lead to action by pediatricists and the Academy of Pediatrics.

S. Z. LEVINE, M.D.

The Pediatrician and the War

Lieutenant Colonel William A. Reilly of Redwood City, Calif., has been promoted to Colonel.

The following Fellows have been released from service with the Armed Forces:

Dr. Harry E. Baldock, Charleston, W. Va.
 Dr. Sidney Blumenthal, New York, N. Y.
 Dr. John E. Brown, Jr., Columbus, Ohio
 Dr. John W. Canaday, Glens Falls, N. Y.
 Dr. Paul D. Clark, Burlington, Vt.
 Dr. Carl L. Cohen, Chicago, Ill.
 Dr. Harold W. Dargeon, New York, N. Y.
 Dr. Max Deutch, St. Louis, Mo.
 Dr. J. Gilbert Eblen, Knoxville, Tenn.
 Dr. Lee E. Farr, Wilmington, Del.
 Dr. Edward A. Hardy, Mt. Vernon, N. Y.
 Dr. Frank D. Hazlett, Washington, Pa.
 Dr. R. R. Hippensteel, Indianapolis, Ind.
 Dr. Louis Judelson, Buffalo, N. Y.
 Dr. W. P. Killingsworth, Port Arthur, Texas
 Dr. Howard T. Knobloch, Bay City, Mich.
 Dr. Robert H. Kotte, Cincinnati, Ohio
 Dr. J. N. Lande, Sioux City, Mich.
 Dr. Harold Lipton, Danbury, Conn.
 Dr. Clarence L. Lyon, Spokane, Wash.
 Dr. John J. Miller, Jr., San Francisco, Calif.
 Dr. Lee Plamer, Louisville, Ky.
 Dr. Mila I. Pierce, Evanston, Ill.
 Dr. Ralph E. Pray, Salinas, Calif.
 Dr. Warren W. Quillian, Miami, Fla.
 Dr. Robert P. Rogers, Greenwich, Conn.
 Dr. Byron K. Rust, Indianapolis, Ind.
 Dr. Robert O. T. Warren, Wilmington, Del.
 Dr. Ernest S. Watson, Elmhurst, Ill.
 Dr. Carl Witus, Detroit, Mich.

News and Notes

The second Annual Lecture in honor of the late Dr. Joseph Brennemann was given on Dec. 27, 1945, at Los Angeles by Dr. Harold K. Faber, Professor of Pediatrics at Stanford University School of Medicine, under the auspices of the Pediatric Section of the Los Angeles County Medical Association. Dr. Faber's topic was "Human Poliomyelitis; Observations on the Portals of Entry and on Their Relation to the Initial Symptoms."

The meeting of Region III of the American Academy of Pediatrics which was to have been held on May 6, 7, and 8, 1946, at the Netherlands Plaza Hotel, Cincinnati, Ohio, has been cancelled.

At the annual meeting of the American Board of Pediatrics the following officers were elected:

Dr. C. Anderson Aldrich, Rochester, Minn., President
Dr. Donovan J. McCune, New York, N. Y., Vice-President
Dr. Lee Forrest Hill, Des Moines, Ia., Secretary-Treasurer (with offices at 3309 Forest Avenue, Des Moines)

Dr. Charles McKhann, Cleveland, Ohio, was appointed to the Board by the Section on Pediatrics of the A. M. A., replacing Dr. F. P. Gengenbach whose term expired.

With the retirement of Dr. C. A. Aldrich, who has held the positions of secretary and treasurer since the Board was started, the office of the Board has been moved to 3309 Forest Avenue, Des Moines, Iowa.

The Board announces the following examinations:

Written Examination—locally under a monitor, March 22, 1946

Oral Examinations—Cleveland, Ohio, April 27 and 28, 1946

San Francisco, Calif.—at the time of the meeting of the A. M. A. (July 1-5) if sufficient applications are received to warrant this examination

At the annual meeting, due to increased expenses, the application fee on and after May 1, 1946, was placed at \$100.

REPORT* OF ANNUAL MEETING OF THE CHILDREN'S BUREAU ADVISORY COMMITTEES ON MATERNAL AND CHILD HEALTH SERVICES AND ON SERVICES FOR CRIPPLED CHILDREN, CHILDREN'S BUREAU U. S. DEPARTMENT OF LABOR

NOV. 8 AND 9, 1945

The meeting was called by the Associate Chief of the Children's Bureau particularly to obtain advice on Senate Bill 1318 (H.R. 3922, H.R. 3994, H.R. 4059) known as the "Maternal and Child Welfare Act of 1945." To this end six committees were appointed from the members of the Advisory Committees to consider on November 8 various aspects of the proposed legislation and report their opinions to the general session of the Committees on November 9.

The reports as modified and accepted or adopted in the general session and a statement by Dr. Eliot are transmitted herewith in accord with the unanimous recommendation of the general session in order to make them available for such use as each member of the Advisory Committees and the Children's Bureau might deem desirable.

*Report prepared by Dr. Allan C. Butler at the direction of the Advisory Committees.

REPORT OF COMMITTEE TO CONSIDER BASIC PHILOSOPHY AND PRINCIPLES
PERTAINING TO S. 1318

This Committee discussed many fundamental principles pertaining to such legislation as proposed in S. 1318.

Certain reservations as regards the jurisdiction of the Federal administrative agency under this bill, its departmental allocation and the integration of this agency, and the proposed maternal, infant, and child medical care program with other Federal health plans were discussed. Before giving critical consideration to the details of the proposed legislation the Committee wishes to make it clear that such consideration does not necessarily constitute an endorsement of the proposed allocation to a bureau in the Department of Labor of authority to develop and direct such an extensive medical care program.

The Committee recognizes the far-reaching and significant contributions of the Children's Bureau to maternal and child health, especially in the fostering of high standards of medical and welfare services. However, in such a program as envisaged in this major step in the development of a Federal Health Program problems of State responsibilities and relationships with Federal agencies are involved which demand consideration of the qualifications of the proposed agency for their conduct and consideration of ability to integrate the proposed program with those for the provision of health and medical services for the remainder of the population.

The Committee recommends that Congress give careful study to the problem of the proper agency to conduct this program and of the relationship between governmental agencies concerned with medical and health services.

The Committee discussed and voted as follows on the following questions:

1. Do we believe that maternal, infant, and child care is in need of better financial support than exists today?

Answer. Unanimously, "Yes."

2. Do we believe that more adequate financial support will of itself provide better maternal, infant, and child care?

Answer. Unanimously, "No."

3. Do we believe that all persons rendering medical services should be remunerated adequately for services rendered including services rendered the indigent?

Answer. 16 "Yes." 1 "No."

4. Do we believe that the medical care of those who are unable to afford direct payment or prepayment for such service is the responsibility of government?

Answer. Unanimously, "Yes."

Disapproval of paragraph (3), page 4, line 3 of Sec. 103 was voted by 10 members, while 6 members voted approval.

The following modification of that paragraph was favored by 14 members and opposed by 3 members.

"(3) provide that as services and facilities are furnished under the plan they shall be available to all mothers and children in the State or locality who are determined by the State health agency to be eligible and who elect to participate in the benefits of the program, and that there will be no discrimination because of race, creed, color, or national origin, and no residence requirements";*

Among the 14 who favored this modification were members who were opposed to the means test in principle, but felt the above modification was essential to a tolerant consideration of such legislation at the present time.

It was also felt by some that if the application of a means test was left to each State that the ultimate development through the Nation of efficient plans for medical care, such as considered here, would not be jeopardized.

*The modification is indicated by the italicized portion.

It was felt by others that this was a wholesome endorsement of State rights under such a program.

There was lengthy debate on the means of protecting medical education and through it the quality of medical care if such legislation as proposed in S. 1318 were enacted. The Committee was in general agreement that careful consideration of the effect of such legislation on medical education and the quality of future medical care were essential if both were to be protected. Though no formal vote was taken, the Committee felt that perpetuation of medical indigency was not a prerequisite to good medical teaching and better medical care.

While no formal expression of opinion was expressed, it was pointed out that provision for the remuneration at the same rate whether the professional services were rendered by groups of professional personnel, including teaching units, or by individuals was desirable both in terms of protecting the quality of teaching service and the interests of individual physicians or other professional personnel.

Designation of members of the advisory committees of the Children's Bureau as individuals representing no organization or as the official representative of an organization was suggested. It was furthermore urged that a member who was designated as the official representative of an organization be given the power of negotiating for that organization.

In the general session November 9 this report was adopted unanimously.

Statement made by

MARTHA M. ELIOT, M.D.

ASSOCIATE CHIEF, CHILDREN'S BUREAU
U. S. DEPARTMENT OF LABOR

At general session, November 9, 1945, of Children's Bureau Advisory Committee on Maternal and Child Health Services and Advisory Committee on Services for Crippled Children and by direction of the Advisory Committees to be attached to the Report of the Committee to Consider Basic Philosophy.

The policies of the Children's Bureau in its administration of the Emergency Maternity and Infant Care program have been referred to a number of times today and yesterday as possibly setting precedents that would not be desirable under a long-time program of services to mothers and children. The Emergency Maternity and Infant Care program was satisfactory only as an emergency program. The Children's Bureau recognizes that in the development of a long-time program, administrative authority of the Federal and State agencies must be clarified and definitely placed. I believe that a long-time program should be State administered. I believe that under the Emergency Maternity and Infant Care program more responsibility and initiative had to be taken by the Federal agency because of the emergency than would be desirable under a long-time program.

I would like to point out that S. 1318 is not an extension of the Emergency Maternity and Infant Care program for the following reasons:

1. The bill provides for an evolutionary development of the maternal and child health and crippled children's programs, State by State, over a 10-year period on the basis of local and State needs and resources for meeting these needs.

2. The bill gives to the States the initiative for development of and the responsibility for carrying out State policies and procedures necessary for the operation of the State plan. The role of the Federal agency would be to establish policies related to minimum standards for care and appropriate use of Federal funds to carry out the purposes of the legislation.

3. This bill makes provision on a legislative basis for methods of maintaining and improving quality of care, which, under the Emergency Maternity and Infant Care program, had to be felt to the Children's Bureau because of the emergency nature of that program.

4. The bill requires the Children's Bureau to obtain the advice of Federal advisory committees, both general and technical, and of the State administrators concerned, before establishing Federal policies to be used as guides in approving

State plans. Furthermore, the bill provides for the same type of cooperation between the State administrative officials and the professional and public groups concerned.

The question of maximum fees to be paid from Federal funds would, of course, have to be discussed and studied by the Bureau with the professional and governmental groups concerned.

The Children's Bureau believes that the program proposed under this bill (S. 1318) would be one essential segment of a national health program and that it can and must be fitted into an over-all medical care program as and when such is developed.

I would like to say further for Miss Lenroot and myself that we would have no objection to the transfer to another department with cabinet rank under conditions that would safeguard the integrity of the Children's Bureau and the services included in the Children's Bureau program. I would like to say further that Miss Lenroot and I would consider transfer of the Children's Bureau to an independent agency without cabinet rank as a great sacrifice for the Bureau.

MAJORITY REPORT OF COMMITTEE ON AVAILABILITY OF SERVICES AND FACILITIES

The meeting was opened by the Chairman reading subsection (3) of Section 103. Title I of S. 1318, the "Maternal and Child Welfare Act of 1945":

"(3) provide that as services and facilities are furnished under the plan they shall be available to all mothers and children in the State or locality who elect to participate in the benefits of the program, and that there will be no discrimination because of race, creed, color, or national origin, and no residence requirements";

The subsection was then opened for general discussion. It was soon evident that there was a rather definite difference in opinion on making the services available to all mothers and children who elect to participate in the benefits of the program.

A number of the medical members present felt that the bill was unacceptable to the medical profession without the inclusion of a means test. To these the provision of services of this kind at public expense seemed an undesirable lessening of individual responsibility. It was brought out that any means test would have to be conducted on a local level and that administrative expenditures varying from 35 cents to 60 cents to 80 cents per family would be necessary to carry out such a test, and that probably in the groups close to the upper limit it might have to be repeated every six months. Some felt that the population could be divided into three classes—one that can afford to pay as they go for their medical care, a second group to which care would be available by prepayment, and finally the so-called medical indigent—and that this bill should apply only to the third group. It was suggested that a means test should be used for corrective medical services and not for preventive services.

Those in favor of the subsection, as read, felt that health like education was something to which every American child and mother during pregnancy and the post-partum period were entitled. That in view of the fact that 85 per cent of the families had an income of less than \$2,500 per year, and 92 per cent less than \$3,000, there would be no great group of children that would be getting this service undeservedly. On the one hand, it was brought out by one member that many people would use this service because they felt it was free. On the other hand, it was brought out that people who could afford to purchase private medical care would do so as indicated by the fact that the charity hospitals the country over were empty because people were able to pay for medical services at the present time.

After a considerable discussion, the matter was finally brought to a vote. The motion was made "That the means test should be used in the administration of the Pepper Act." The vote was 5 for the motion, and 8 against the motion.

In view of the fact that there was considerable opposition to the motion the Chairman suggested to the minority that they hand in a minority report.

The matter of availability of administrative and other facilities was discussed. It was particularly emphasized and brought out by Dr. Getting that the inauguration of a program under this bill would necessitate in the State of Massachusetts an increase of 75 times the work necessary in his department, and it was brought out that in the inauguration of any program it would of necessity be very gradual in getting under way.

It was further suggested that in view of the difference in medical facilities in various States and with the appropriation of funds by different States it would be necessary to see that individuals from one State could not avail themselves of services in another State and then return to their former homes. It was moved and seconded that by adding the words "domiciled in the State or locality" after "mothers" in subsection (3) this might be corrected. The motion was passed.

In the general session November 9, this report was adopted 29 to 16. The minority report follows.

MINORITY REPORT

The minority group of the Committee on Availability of Services and Facilities dissents from the report of the majority on the issue of providing a means test to determine eligibility of individuals or families for participation in the services provided under proposed Bill S.1318. The minority believes that to offer medical service to all, regardless of economic status, in any population group, is an unwise procedure because:

1. It encourages excessive dependence upon government and discourages individual self-reliance.
2. It tends to congest services intended primarily for the underprivileged and thus to deprive them of full benefits.
3. It places a needless and undesirable burden upon taxpayers, especially small taxpayers least able to bear it.
4. It competes unfairly with and tends to discourage established private and semi-private agencies already rendering meritorious service.

The majority believes in a suitable means test, to be determined at State levels after consultation with appropriate official and social service agencies and medical societies, applicable to medical care aspects only and exclusive of established public health procedures and diagnostic services in preventive medicine.

REPORT OF COMMITTEE ON METHODS OF REMUNERATION FOR PROFESSIONAL SERVICES

- (1) This is a suggested change to the wording of lines 9-13, page 6, Sec. 103:

"... payments to individual physicians and other professional personnel for care furnished under this title on a per capita, salary, per case, per session, or fee-for-service basis or any combination of these bases, the methods and amounts to be determined by the State agency after consideration with the professional groups or institutions rendering the service, provided further that such professional personnel, groups or institutions do not accept supplemental payments."

- (2) We recommend that careful consideration be given to financial participation by the State where supplemental payments appropriate to differential standards of living are involved.
- (3) It is moved to make the same changes on page 15, lines 15-18, as made in Sec. 103, page 6, lines 9-13.
- (4) We recommend that in computing per diem cost for each hospital for reimbursement under this program, the basis be the cost of standard nonluxury accommodations.

In general session November 9, this report was adopted unanimously.

REPORT OF COMMITTEE ON SCOPE AND EXTENSION OF SERVICES AND METHODS OF
COORDINATION WITH OTHER MEDICAL CARE PROGRAMS

The Committee directed its discussion to the principles which should be considered in reviewing the provisions of S.1318.

Requirement for Development of Services and Facilities Within Ten Years.—The Committee is of the opinion that designating a specific period of time has constructive value, and that it is reasonable to talk in terms of ten years. What is to be in effect at the end of the ten-year period must be defined in terms of what can be accomplished, taking into account all of the difficulties involved particularly those of obtaining trained personnel. This must be worked out by each State in its own particular terms.

Each State will be responsible for setting up its own plan, outlining how it proposes to reach the goal. To comply with the provisions of the bill as now written, this plan would have to be within the range of the facilities and services described in Sections 101 and 201. The Committee recognizes that States will move at different rates in relation to the various aspects of these services. However, one area of the State cannot be well served while another is left without service. Therefore, the Committee feels that availability of services and facilities on a State-wide basis 10 years after approval of the State plan is essential to a satisfactory State program.

The ten-year goal should be defined in general terms. It should not be written more specifically into the law than it is in S.1318. It should be possible after several years of experience to revise the statement of the goal. The advisory committee could at that time consider the problem and make fresh recommendations to the Bureau.

It is recommended that the ten-year period should be extended in the case of a State which offers an adequate reason for planning over a longer period, and shows evidence of continuous progress.

Services Outlined in S.1318 Adequate.—The description of services and facilities in Section 101 seem adequate. The words "preventive health work and diagnostic services" found in Section 101 should also be included in Section 201. This is a matter of emphasis, in order that this important phase of the program be given equal consideration with the curative and corrective services.

The words "dental care" should be added wherever appropriate to make clear that both medical and dental services are covered. Specifically, this should be done in the following places: Lines 14 and 23, page 5; lines 10 and 16, page 6; lines 3 and 9, page 7; line 3, page 11; and line 13, page 15.

The Committee recommends that appropriate language be inserted in the bill to clarify that the words "clinic and health service agency" include groups of physicians or dentists, to assure their inclusion in providing service in the States.

It is the consensus of the Committee that a child should be considered as a child until 21 years of age for child health and crippled children's services. This should be a maximum and not an obligatory age. Since the purpose of a lower age is frequently to avoid duplication of services, it is recommended that there be incorporated in the bill appropriate language to direct agreements governing the relation of these services to such other services.

Administration at the State Level.—The Committee supports the proposal in the bill that services for crippled children be administered or supervised by the State health agency after a date to be specified in the bill. The Committee recommends that the Children's Bureau formulate a statement of the reasons why this is desirable, to be submitted as part of its testimony at the hearings, and for such other use as is appropriate.

Coordination of Federal Programs.—It is the consensus of the Committee that the medical care program for mothers and children as set forth in S.1318 is a partial program. It is partial in that there are related services currently administered by other Federal agencies, such as the United States Public Health Service, the Office of Education, Vocational Rehabilitation, and Social Security Board. It is also partial in that there are services still not provided from any source.

The Committee believes that there is an obligation on the part of all Federal agencies having related interests to arrive at common standards of administration, personnel, evaluations of service, policy, costs, etc. There should be a unified approach to the States as far as possible. It is recommended that the Children's Bureau accept this obligation and act on it to the fullest extent possible, and enter it into the record of the hearings on this bill.

In general session November 9, this report was adopted unanimously.

REPORT OF THE COMMITTEE ON RESEARCH PROJECTS AND METHODS OF
ESTABLISHING STANDARDS OF CARE

Research is so basic to the efficiency of any program for maternal and child health that this committee recommends:

That much larger funds should be allocated to research than are provided in the Bill S.1318 or than have been available to the Bureau in the past.

Such funds are to be available to the Children's Bureau for such purposes as:

1. To undertake with its own personnel only such projects as can be best studied on a national scale; for example:
 - (a) The evaluation of previous programs, such as maternal and infant mortality under the EMIC program, as a basis for administration of present and future programs.
 - (b) A study of the effect of prolonged institutionalization on mental, physical, and social development.
 - (c) Determination of the incidence of epidemic diarrhea in the newborn; methods of its prevention and control.
 - (d) Evaluation of the facilities for the proper care of mental defectives.
 - (e) In cooperation with other Government agencies, study of the incidence of poisoning of children by household products and methods of general education as to their dangers.
2. Allocation to medical schools or other organizations for specific research projects.
3. Coordination of the results of significant research studies throughout the world dealing with the problems of maternal and child welfare.

The committee recommends that the Children's Bureau establish a special advisory committee on research to aid them in the use of such funds as become available.

It is recognized that for the proper implementation of the program and advancement of public health, proper standards of care should be established and maintained. The committee believes:

That the paragraph related to this subject, in Bill S-1318, page 14, line 12, section B, reading:

"standards for professional personnel rendering medical, dental, nursing, and related types of care or service and standards for hospital and other institutional care and services, such standards to be established by the State agency after consultation with professional advisory committees appointed by the State agency,"

should be modified by the addition of the phrase:

"provided that these standards are not below certain minimum requirements set by the Children's Bureau after consultation with its advisory committee."

In general session November 9, this report was adopted unanimously.

COMMITTEE ON PROGRAMS OF PROFESSIONAL EDUCATION AND TRAINING

The Committee are agreed that the education and training of professional personnel must be of the highest quality, that they must be progressively improved, and that any legislation which violates these fundamental principles is undesirable.

As Bill S.1318 and similar legislation now stand, they may curtail teaching services. The Committee, while recognizing this threat to medical education, was unable to reach a conclusion as to how to avert it, particularly in the field of clinical obstetrics. However, to this end the following suggestions are made:

That payments to hospitals shall be limited to those institutions in which the medical, nursing and all other professional services meet acceptable standards. Hospitals and other services staffed by qualified personnel would improve the educational facilities and thus the opportunities available to professional personnel as well as provide better care for the patient. The use of unqualified or partially trained personnel is detrimental to any health program and not in the public interest.

Professional fees should be paid to teaching departments rendering services under the bill at the same rates as paid for services rendered by individuals or other professional groups.

It is the feeling of this Committee that until such time as there are available hospitals and facilities with sufficient qualified professional personnel to serve all regions in the United States, the services of qualified nurse-midwives are needed in some areas, provided they work under competent medical supervision with availability of hospital care as needed. To this end, training facilities for nurse-midwives should be expanded.

The Committee recommends that a portion of the appropriated funds be made available for the professional education of personnel; these funds to be expended to compensate accredited institutions for teaching and supervision and for scholarships to returning veterans and others in order to supply qualified personnel to regions in which they are needed to promote better maternal and child care.

Committee Members Present:

Dr. Fred Adair
Miss Kathleen Allen
Dr. Sterling H. Ashmun
Dr. Carl E. Badgley
Miss Bernadette Banker, R.N.
Dr. W. W. Bauer
Dr. Leona Baumgartner
Dr. Jessie Bierman
Dr. M. O. Bousfield
Dr. James Barrett Brown
Dr. Robin C. Buerki
Dr. Allan M. Butler
Dr. George D. Cannon
Dr. John W. Chenault
Miss Hazel Corbin
Miss Ruth Council
Dr. M. Edward Davis
Dr. W. C. Davison
Dr. Robert L. DeNormandie
Dr. Nicholson J. Eastman
Mrs. Gertrude Folendorf, R.N.
Dr. Louise Galvin
Dr. Harvey F. Garrison

Dr. Franklin P. Gengenbach
Dr. Stanley Gibson
Dr. Arthur Bruce Gill
Dr. Eleanor Harvey
Dr. Henry F. Helmholtz
Miss Ruth Houlton, R.N.
Dr. T. Duckett Jones
Miss Isabelle Jordan, R.N.
Mrs. Mary Wysor Keefer
Dr. George Kosmak
Dr. Leon Kramer
Mr. Lawrence Linck
Dr. Francis E. Lord
Miss Mary MacDonald, R.N.
Dr. Basil MacLean
Dr. Alexander T. Martin
Dr. Alice F. Maxwell
Dr. Oscar L. Miller
Dr. Oren Moore
Miss Olivia T. Peterson, R.N.
Dr. Alice M. Pickett
Dr. E. D. Plass
Dr. Grover F. Powers

Dr. John Z. Preston
Dr. Ruth Raattama
Dr. Edward S. Rogers
Miss Marion Sheahan
Miss Ruth Sleeper, R.N.
Dr. Francis S. Smyth
Miss Mabel Staupers, R.N.
Dr. George Stevenson
Miss Jessie Stevenson, R.N.

Miss Isabelle Stewart, R.N.
Mrs. Zephyr Holman Stewart
Mr. R. C. Thompson
Dr. S. A. Thompson
Dr. Felix Underwood
Dr. Joseph S. Wall
Dr. Philip F. Williams
Dr. James Wilson

Guests:

Dr. Walter L. Bierring
Dr. Otto W. Brandhorst
Dr. Kenneth A. Easlick
Dr. Vlado A. Getting
Dr. John P. Hubbard
Miss Kate McMahon
Dr. Duncan Reid

Dr. I. C. Higgin
Dr. Isaac Schour
Dr. J. E. M. Thomson
Miss Lute Troutt
Dr. R. M. Walls
Dr. Wm. C. Webb, Jr.

Comment

ANNUAL MEETING AT DETROIT

Owing to the closeness of the time of the Annual Meeting to the dead line for closing forms for the February JOURNAL, the full report of the Fourteenth Annual Meeting in Detroit, Jan. 15-18, 1946, will not appear until March. Certain committee reports and the regional reports which were available previous to the meeting appear in this issue. There was a large attendance and many were present who had only recently been released from military service.

In addition to a day of clinics at Detroit hospitals, the scientific programs were excellent and well attended.

Two matters, however, overshadowed the meeting. One was the report of the Committee on the Academy Study of Medical Care for Children. This was presented to the Academy as a whole and at a dinner meeting to the State Chairmen, upon whom much of the actual work will fall. The feeling of everyone was that the Academy has undertaken a tremendous task, a far greater one in its development than was in the mind of anyone when the study was voted at the meeting in St. Louis in 1944. The Academy is committed to the study which is well under way and it must be carried through. As every one realized at Detroit, it will mean work and time on the part of every member if worth-while results are to be obtained.

Overshadowing all else was the question of Federal legislation in the field of medicine. Perhaps too much discussion was directed to past history. The important thing is that a number of bills are before committees in Congress and the medical profession must constructively criticize the proposals, pointing out the changes which are necessary before the proposals are not only acceptable to the medical profession, but also will bring about the objectives of the bills. There was an almost unanimous opinion that the Pepper bill as now written will not bring about improved medical care for children. At the final session a rather general resolution was passed stating the attitude of the Academy on Federal legislation, and a secondary resolution stating thirteen points or objections to the Pepper bill. The resolution adopted is as follows:

RESOLUTION ADOPTED BY THE ACADEMY JAN. 18, 1946

The American Academy of Pediatrics in annual session at Detroit, Mich., Jan. 15-18, 1946, after careful consideration of proposed legislation in Congress as it relates to child health services reaffirms its resolution as adopted at its 1939 session, namely:

"That the American Academy of Pediatrics, regarding the provisions for maternal and child welfare, favors the use of public funds to provide *such services to those groups of the population unable to pay for medical services*, to the end that the standards or medical care may be maintained at a high level among such groups."

The Academy of Pediatrics does not favor the use of Federal funds for those able to provide good medical care from their own resources.

The Academy directs the attention of those considering proposed legislation to its fact-finding study of child health services now in progress which, at its conclusion, should assist in the development of sound programs at state levels based on demonstrated needs.

Pending the completion of this study, it is recognized that urgent needs exist in some states that should be met in the immediate future. To this end the Academy recommends that additional Federal funds be made available for grants-in-aid to the states under existing Maternal and Child Health and Crippled Children's programs of Title V of the Social Security Act as amended in 1939.

The Academy would welcome the privilege of sending representatives now or at any time to confer with those responsible for the preparation of legislation pertaining to child health.

The supplemental resolution adopted was as follows:

The American Academy of Pediatrics makes the following specific criticisms of S. 1318.

1. The bill as now written states that services and facilities furnished under the state plans are to be available to all mothers and children who elect to participate in the benefits and therefore denies to the States the right to determine eligibility.

2. The bill excludes fee-for-service as a means of paying practitioners for service rendered.

3. The bill makes inadequate provision for paying groups of physicians or institutions for professional services rendered.

4. The bill does not specify that professional personnel, groups, or institutions do not accept supplemental payments.

5. The bill endorses the Children's Bureau as the most suitable administrative agency of this major step in a National Health Program without assuring integration of the administrative functions and health services under this bill with other health activities of the government.

6. The bill does not satisfactorily define the Federal or State advisory committees as regards personnel, method of appointment, advisory and policy making roles, or manner of giving authority to the record of consultations with and recommendations to the administrators at Federal and State levels.

7. The bill makes no provision for variation in remuneration for service according to the differing costs pertaining in various states.

8. The bill makes no provision for the prevention of arbitrary requests on short notice by the Federal administrative agency for reports from the State health agencies and similarly arbitrary requests by the State health agencies for reports from those rendering services.

9. The provisions for handling claims are unsatisfactory.

10. The bill fails to specify adequately reference to coverage of dental care in appropriate portions of the bill.

11. The bill makes no adequate provision for the protection of the well-organized and integrated teaching services on which the future quality of medical care is so dependent.

12. The bill makes inadequate provision for the support and encouragement of research pertaining to the improvement of maternal and child health services and medical care.

13. The bill makes no provision for assuring that State plans be expanded at rates that do not exceed available administrative and professional personnel and resources and that assurance against too rapid expansion be considered as one of the criteria of approval of a State plan by the Federal agency.

For these reasons the American Academy of Pediatrics believes that the Maternal and Child Welfare Act of 1945 (S. 1318) does not represent the best form of legislation for the purpose for which it was written.

At the Business Meeting on Friday, January 18, Dr. Edwards Park of Baltimore was awarded the "Borden Award." The "Mead Johnson Awards" were not awarded this year.

Dr. Jay I. Durand of Seattle was elected president for 1946 and Dr. Lee Forrest Hill of Des Moines, vice-president. Dr. George F. Munns of Winnetka, Ill., was elected to the Chairmanship of Region III.

A special committee on redistricting the Academy, changing the present four districts to nine, was presented for study and action at the next Annual Meeting.

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Original Communications

PRESIDENTIAL ADDRESS

JOSEPH S. WALL, M.D.
WASHINGTON, D. C.

IF BREVITY be the soul of wit, it was badly mauled during yesterday's presentation before the Academy of legislative proposals now in the offing! The following presidential address, required by custom of the Academy, shall be characterized by the presence of that soul even though lacking the corpus which is its normal habitat.

It usually gives one a pleasurable sensation to hear or read something nice said about his profession, such as the sentiments expressed by Robert Louis Stevenson, who knew intimately both the heights of literary achievement and the depths of physical misfortune, during which he learned much of medicine and more of its disciples. Of the latter he writes:

"There are men and classes of men that stand above the common herd; the soldier, the sailor and the shepherd not infrequently; the artist rarely; rarer still, the clergyman; the physician almost as a rule."

Without assuming for our Fellowship any spirit of egotism or of self-praise, we believe that the specialty of pediatrics together with its adherents may, in the broad field of medicine, more especially merit the attribute ascribed by Stevenson to workers in the healing art.

There is an intangible something about pediatrics and pediatricians which seems to place upon both the stamp of humanitarianism with more than a modicum of professional gentleness and gentility. Perhaps it is a reflection of the engaging frankness and honest amiability of children with whom we work, who are inherently blessed with the joy of living and who may infect us in turn with a measure of good cheer and optimism.

We may credit our specialty of pediatrics with a degree of altruism not exceeded and rarely equaled by any other specialty in medicine.

You, and your antecedent founders, many of whom have passed to their last reward, have builded soundly and intelligently a structure of preventive medicine which should prove a model for all whose efforts are to reduce rather than to relieve ill-health.

Periodic health examinations are to you so commonplace and bulk so largely in the scope of your practice that some days may pass when you are even

denied the function of healing the sick, while you romp through the green pastures in which you assist and watch fascinating young saplings go through their paces of growth and development. One might even say that the scope of pediatrics is greater in health than in disease.

The social aspects of pediatrics have long engaged your interest, even latterly occupying an important space in the scientific columns of the official organ of the Academy, the *JOURNAL OF PEDIATRICS*.

Your many and diverse committees have continued to function successfully amid the vicissitudes of war, although at times their work has been limited by absence of members and pressures of civilian demands.

Time must limit the mention of all the activities of the past year, but the work of certain committees demands especial reference.

The Committee on Governmental and Medical Agencies under the chairmanship of Dr. Stanley Nichols has enlarged its scope to include certain collaborators from the American Medical Association, the Children's Bureau, and the United States Public Health Service. Its functions will no doubt broaden much in the future because of the present and contemplated participation of government in the practice of medicine which may expand to an extent not now predictable. Already the committee is engaged in aiding the Food and Drug Administration of the Department of Agriculture in devising ways and means of protecting children from the use of harmful drugs exploited through improper labeling and advertising.

The Committee on Immunizations and Therapeutic Procedures, under the chairmanship of Dr. John Toomey, periodically revises its publication, which has become one of the Academy's best sellers to many organizations and medical schools, aside from its distribution to the membership.

The Committee on Pan-American Scholarships, Dr. Henry Helmholtz, chairman, continues to bring to this country bright young pediatricians from our sister republics to the South who, in turn, disseminate the newer knowledge of pediatrics on their return to their native countries, wherein they form the cells and nuclei which make for growing interest in the Academy and for extension of its membership among all of the Latin-American Republics.

We should be most remiss should we fail to mention the Committee on Geographical Distribution of Pediatricians. Although long in name, this committee is short in numbers, having but one member, Dr. Otto L. Goehle of Ohio. The solo feat of this one-man committee, which should serve as a stimulus to committeemen and committeewomen who share their burdens with others, was the production of a report and atlas upon all the practicing pediatricians in the United States, by State and by individual locality.

Dr. Goehle has studied and charted the population in the States, its increase in a five-year period, the total number of physicians per State, of Fellows of the Academy, and of Diplomates of the National Board—a stupendous piece of work which should prove of great value to our postwar committee in its present researches and should receive our grateful appreciation.

The Committee on Liaison with the American Legion, with Dr. Edward C. Mitchell as Honorary Liaison and Dr. Hugh McCulloch as Chief Liaison Officer,

has actively renewed its cooperation with the Legion. Miss Emma C. Puschner, the indefatigable executive of the Legion's Child Welfare Division, has directed much of her time and remarkable energy to cementing closer relationship between the Legion and the Academy.

Dr. Irvine McQuarrie, chairman of the Committee on Post-War Courses in Pediatrics, had scarcely embarked on an extensive study and survey of the facilities for aiding returning veterans when the sudden termination of the war precipitated a crisis which the committee has worked assiduously to meet. The Academy's central office is now equipped with space and secretarial help to offer every aid possible to veterans now or about to be released, who are thirsting to refresh their minds through clinical experiences in pediatrics. Unfortunately, the number of residencies available for those who seek them, especially veterans whose training in pediatrics has been interrupted, has been limited, but concentrated "refresher courses" are now being formed to meet the needs of many.

In this connection, it is stimulating and encouraging as we look into the future to realize that our specialty of pediatrics still has the ability to woo the interest of young physicians who have spent the last few years solely in the environment of adult medicine and surgery.

You will have heard in detail the report of progress being made by the Committee on Post-War Planning under the chairmanship of Dr. Warren R. Sisson, which is now fortunate in possessing as its executive director a Fellow of the Academy, Dr. John P. Hubbard, who brings to it not only the experience of a skilled pediatrician but that of an administrator as well. The original budget of \$8,000 appropriated by the Executive Board to initiate the postwar study was generously matched by an equal amount through the good offices of Mr. A. L. Rose of the Mead Johnson Company to whom we would express our grateful appreciation.

In accordance with the request of the Academy for aid and cooperation in the survey and study being conducted by this committee, Dr. Martha M. Eliot, Associate Chief of the Children's Bureau, assigned Dr. Katherine Bain, Director of the Division of Research in Child Development, to lend assistance. Dr. Bain has devoted practically her whole time to the work at hand, having been largely instrumental in the formulation of the detailed schedules concerned with the investigations now in progress.

We would express our deep appreciation, also, to Surgeon General Thomas Parran of the United States Public Health Service for his generous assignment of Dr. Charles Williams, Jr., and Dr. Joseph Lachman to whole-time service as aids to the committee, aside from designating other skilled members of his staff in the capacity of consultants and analysts of the material produced by the study.

The instant and wholehearted assistance of these two Federal departments represents a contribution of expert help, far beyond the monetary values involved in the utilization of their services, and receives from the Academy its deepest gratitude.

At the invitation of the president of the American Board of Pediatrics, composed of three members appointed by the American Pediatric Society, the Section on Pediatrics of the American Medical Association, and the Academy of Pediatrics, we had the privilege of attending as an observer the last examination conducted in Atlantic City in early December. This occasion was one of great interest to me as I was impressed with the fairness and justice displayed by each and every examiner, who sought to become *en rapport* with the examinee by a sympathetic approach which endeavored to place the candidate at ease as best one could under rather hypertonic circumstances. The scope of the questioning was such as to bring out beyond peradventure the qualifications of a candidate for certification as a diplomate of the Board.

It is with especial pleasure that the Academy welcomes back its many members who served their country in the Armed Forces during the war. Many of them at great personal sacrifice answered the call of duty in this and in foreign lands. To them we would give every acclaim and felicitation within our power to bestow.

We would take this occasion to express our heartfelt appreciation of the aid and loyalty accorded us during our term of office by the officials of the Board, especially by Secretary Grulee, the Regional and State Chairmen, and by the membership of the Academy at large.

In the past, your officials who are ever-solicitous for the interest of pediatrics and pediatricians have endeavored to play the part of conciliators and peacemakers in any controversies arising with certain branches of the Department of Labor, which recognizes conciliators as necessary adjuncts to the amicable solution of disputes.

Your officers, in the role of peacemakers, always a dangerous occupation, have occasionally been belabored from within the Academy ranks for being asleep on the job; as being guided by emotion and as failing to present vigorously the viewpoint of the Academy; as always speaking in a destructive and not in a constructive way; and as precipitating "brawls" of various kinds. From officialdom, we have been criticized for speaking out of turn concerning the sentiments you commonly and as a majority embrace; for presenting viewpoints which should be left to the Academy to express; for rushing into print and by implication, at least, that our criticism of a government bureau would have been far less drastic were it largely staffed by men instead of women. That such a sentiment should even be entertained reflecting on the inherent gallantry of any pediatrician, God forbid!

Your officials have devoted much time and effort toward peaceful and conciliatory solutions of differences arising with governmental agencies. In some they have been successful, in others their frustrations have been as many as those of which Freud writes, but we are "soothed and sustained by an unfaltering trust" in the promise of ancient Scriptures that: "Blessed are the peacemakers for they shall be called the children of God"!

THE MOVEMENT IN MEDICAL ECONOMICS

NATHAN SINAI, DR.P.H.

ANN ARBOR, MICH.

TO THOSE who would study a social movement, the panorama of episodes and events in medical economics offers abundant material. The roots of the movement reach deeply into a century and a half of history; they are solidly imbedded and draw their substance from two great achievements of man.

Both achievements are described as "revolutions." The one, the Industrial Revolution, resulted from man's success in harnessing inanimate power. It has brought untold benefits but it has brought, also, acute problems of adjustment. At the very core of these problems is the adjustment to the need of *earning* a living rather than *making* a living—the process of transforming work into a medium of exchange in order to secure the goods and services necessary to a satisfactory existence. And out of this there emerge the problems of and the emphasis upon "security."

The other revolution, the Medical, resulted from man's success in the organization and the refinement of the medical sciences. Out of this process, defined as Research, have come enormous benefits and, likewise, acute problems of adjustment. Primarily, the questions here concern the ways and means of utilizing the abundant products of science. The two revolutions touch at many points but it is at this one that they become indivisibly joined to produce the problems, the research, the principles, and the practices of medical economics.

As a complementary statement it should be emphasized that neither the Industrial nor the Medical Revolution shows signs of a diminishing tempo. The current happenings, therefore, must be viewed not as distinct incidents in medical economics but as related episodes that portend continuing events.

Look back over the span of a decade. Compressed within the short period is a series of notable medical economic phenomena. All of them express either the need or the demand of larger or smaller groups of the population for the benefits of the health sciences.

Sharply outlined against the depression has been the relatively enormous growth of services for the less-favored groups of the population. Farm Security, medical relief, widows, orphans, the crippled, the aged—these are certain of the categories for which plans and programs have been developed. The categories are old; the semblance of a more orderly national, state, and local approach toward solutions is new.

For the more favored population groups—those that are self-supporting—the variety of plans almost defies any orderly arrangement. They number into the hundreds and include Blue Cross and other hospital programs, those sponsored by medical societies, those offered by insurance companies and the many other plans sponsored by government, by industry, by medical groups or by consumer groups.

Presented before the Fourteenth Annual Meeting, American Academy of Pediatrics, Detroit, Mich., Jan. 17, 1946.

Viewing the development as a whole certain significant features become evident. Whatever may be the differences between plans all present one characteristic that is common. All present an easier form of payment for the services that are included in a given plan. This feature, combined with the evidence obtained from public polls and the better evidence of the response to the plans themselves, indicates what is the primary public interest in medical economics.

The other significant aspect involves the trend that marks this development of a decade. With only minor exceptions the plans offered to the public are of a limited type. The limitations present many variables that relate to services, to geography, to age groups and others. The trend, however, is toward the reduction of limitations and this trend may be interpreted either as a response to public demand or a growing recognition of public need.

These observations of significant features lead to the conclusion that the movement in medical economics is toward prepayment or a form of pooled payment for what, ultimately, will become comprehensive health services. Viewing incidents or episodes it might be concluded that the movement is a chaotic one but, viewing the whole over a period of time, all of the episodes fit into a rather orderly pattern. Prepayment is linked to the problem of security in earning a living; comprehensive services are joined to the problem of distributing the abundance of science. And whether it be a medical society plan, a Blue Cross plan, a Pepper bill or a Wagner-Murray-Dingell bill the pattern of purposes does not change.

The evolution of professional attitudes toward medical economic problems in the United States presents some impressive changes. The principle of prepayment was the first issue. The principle was opposed, then its application was approved on a localized basis, then the approval was expanded to a state-wide program and now the principle of an interstate or national health plan under professional sponsorship is under consideration. And, at the same time, consideration is being given to the inclusion of more comprehensive services. Again, the pattern of action conforms.

The chief issue in the United States today is not prepayment; it is not the question of comprehensive services; nor is it the question of a national health program. The issue is the organization and administration of a national health program—a program with either limited or comprehensive services and population coverage; a program that utilizes the principle of payment from a pool of funds for whatever services are included. It is regrettable, therefore, that so much passion is exhibited on secondary questions and so little energy is expended on the problems of organization and administration.

Any national health program, whether it be voluntary or compulsory, will face problems of organization and administration. The first problem involves the maintenance of a reasonable balance between the responsibility and the authority granted to the central agency. If the responsibility for making a system work is weighty, so must be the authority. If administration is to develop as an orderly procedure, guiding standards and rules and regulations must be adopted. It is true that administration calls for a certain degree of flexibility and a reasonable balance between central and local authority. The tendency, however, is to concentrate attention upon the danger of central authority. Too

often is it forgotten that the one element that can wreck a national health program as quickly as arbitrary central authority is irresponsible state or local authority which, insisting upon autonomy, refuses to adhere to the agreement of the majority. Whether the central agency is that of a voluntary health plan, a Children's Bureau or a United States Public Health Service the principle of balanced responsibility and authority holds.

A second major problem concerns the adequacy of payment. Usually the discussions of this question involve both the amount and the form of payment. In recent years there has been a broad education on the subject of price controls—of price “floors” and price “ceilings.” As is natural, perhaps, the buyers of goods or services insist upon price ceilings; the sellers, upon “floors.” But there is also the general realization that for the public good neither buyers nor sellers should be given the uncurbed privilege of establishing only a ceiling in the one case or a floor in the other. And in this connection careful consideration should be given to any proposal to establish a “means test” for any large percentage of self-supporting people. Whether it is called a means test or concealed in a cash indemnity system is a minor matter as far as public reaction is concerned. “Cash indemnity” is that form of payment that establishes no ceiling and is an invitation to added charges. It violates the very principle of prepayment.

Inevitably the issue of payment for services raises the question of controls. It is one of the unfortunate results of misunderstanding that control devices are interpreted as attacks upon integrity. Yet without some control of the minority—be it a minority among subscribers, physicians, hospitals or other personnel or agencies—the economic solvency of any national health plan is endangered. To say that if there are more services than funds, the funds will be prorated evenly is to lean upon a weak device. Its one certain result is a series of questionable increases in rates or costs. Or, to say that, if solvency is endangered, levies of fees or partial fees may be made upon patients, likewise dodges the issue of control.

Adequate administration calls for adequate control in the interests of the great majority of physicians, of hospitals, of patients. In devising measures of control one principle must be emphasized—the measures must not be burdensome or irritating to the majority for whom no measure is needed.

Attending the consideration of the forms of payment there is much confusion because of the mixed motives and purposes that underlie many of the discussions. The forms are described, usually, as fee-for-service, capitation, salary, or any combination of the three basic types. Payment “per case” is a variation of the fee-for-service and payment “per clinic session” is a variation of salary.

If ease of application and assurance of solvency were the only considerations, payment on a per capita basis or by salary might appear to be the choice of the administrator. The arithmetic of each presents itself as a simple multiplication without any problem of last-quarter deficits. On the other hand, the average physician looks with disfavor upon a form of payment other than the fee-for-service. The method is within the framework of his experience; he accepts and supports it against a change to something which is unfamiliar.

Since only passing references are made to salary payments the choice for the

general services of individual practitioners appears to lie between capitation and fees for services. The chief source of experience with capitation is the British scheme of health insurance, which provides only the services of general practitioners, excluding maternity services.

Much more discussion of capitation payments for general services in a system that also includes specialists' services is warranted. The method requires a definition of general practitioners' services; it also requires consideration in terms of the existing conditions of American medical practice. Rightly or wrongly, there are no legal curbs to specialization in the United States. Many general practitioners provide surgical, obstetric, pediatric, and other services. Under such conditions many general practitioners might occupy a dual position, receiving a capitation payment for one list of services and fees for another. If it is assumed that special services will be provided only by those who have been certified by the various boards, an analysis of the medical personnel available in a cross-section of communities will dispel the belief. The purpose in stressing these aspects of capitation is to raise the questions of administration and, at the same time, to stress the point that there are very few methods in medical economics that may be painted as either all black or all white. To accept capitation payment without critical analysis is neither more nor less permissible than its rejection only upon the basis of unfamiliarity.

Neither black nor white is payment on a basis of fees for services. This method appears to be the American choice and it should be emphasized again that payment for a defined case—a surgical case, a maternity case, well-baby services over a period of time—is only a variation of the fee-for-service.

The fee-for-service will not work merely because enthusiastic resolutions endorse it. The method has a long history of failure when applied over a sufficient period of time and especially when it is used to pay for general services. It will work only if it is made to work through buttressing it with forthright methods of control. In choosing controls the principle mentioned previously should be applied but, more than this, the controls themselves must have strong professional support as a protection both to the public and the profession.

Closely related to the issues of organization, administration and payment is the quality of the services. On this subject there have been many loose and confusing utterances. Generalizations about quality, like the usual generalizations, display only an impressive cadence.

Too often quality is presented and discussed as though it were a single element instead of one of the most complex compounds. It is a tribute to the Academy that it is now undertaking the hard task of developing standards against which the quality of pediatric services may be measured. None of the committee members or the technical staff will underestimate the proportions of the necessary work.

Quality is a compound made up of many variable components. Obviously physical facilities—hospitals, beds for special types of cases, equipment—present only one of the variables. A second component would include personnel—general practitioners, certified specialists, uncertified specialists, nurses, and others. It is unnecessary to stress the variability of this component. In spite of extreme variation it is relatively easy to obtain information on these aspects of

quality. Out of such studies conclusions may be drawn on the distribution and possible adequacy of physical facilities and their utilization. Likewise conclusions are possible concerning the distribution of personnel and the utilization of their varied services by all or a portion of the population. But too often the attempts to establish standards of quality stop at this point—the point at which the analysis of the dynamic aspects of the subject might start.

In a specific case the quality of the service that may be rendered is related directly to the physician's scientific knowledge. Therefore, any study of the potential quality that may be available must include an evaluation of this knowledge, measured against an acceptable standard. At the same time, it is recognized that a gap may exist between what the physician knows and what he applies. The factors responsible for the gap call for critical analysis.

This sequence of steps indicates the necessary content of anything approaching a conclusive study of quality. Only a few such studies have been made, but each one serves as weighty evidence of the need for more. The studies of maternal mortality, on an individual case basis, by the Academies of Medicine in New York and Philadelphia are good examples. And two other studies made in Michigan produced significant results. One was a study of the postgraduate needs of general practitioners in which the knowledge of the physician was related to his year of graduation from medical school and his efforts to acquaint himself with the advances in medicine. In this study 438 physicians divided into groups that were graduated in 1910, 1920, and 1930 submitted to an examination and each gave information concerning his postgraduate efforts.

The other study, under the Committee on Maternal Health of the state society, was an analysis of the quality of the maternal service received by over 10,000 patients delivered in a period of three months. The data were obtained from the physicians who attended the births; it was a study of the practices applied in obstetrical cases, and those practices were measured against standards that were adopted by the Committee.

This stress upon the methods of arriving at a conclusion on the subject of quality shows the fallacy of direct comparisons, because of meager knowledge, between this country and others, or between two or more areas in this country. No comparison of any type will be productive except, ultimately, the comparison between what service is rendered and what service should be rendered. In short, the study of quality is valuable only as a preliminary step to improvement. And improvement calls for an emphasis upon basic training and effective postgraduate education as well as an attack upon the social and economic obstacles to the highest quality of service.

The movement in medical economics may be described as one that has breadth, depth, and speed. It is the last characteristic, speed, that makes a concentrated attention to the methods and problems of administration so vital. Only a few of the problems have been described, but enough has been said to show what is the greatest need of all, the need of dispassionate analysis. Nothing is gained and precious time is squandered by the confusion of personalities with principles and by the tendency to think in terms of absolutes. The movement calls for more than that; it lends itself to objective scientific consideration; it demands and deserves objective consideration by scientists.

FACTS AND FIGURES IN PEDIATRIC MEDICINE

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MEMBERS of any profession are interested in tools, techniques—the ways and means by which they can better themselves. Statistics giving techniques for interpreting and thus using the facts and figures issuing as data from professional activities is a very powerful tool in the hands of the profession equipped to use the tool intelligently. In developing this paper I am endeavoring first to present to you facts and figures which are of interest to pediatricians and second to give you insight into the most frequently available techniques, illustrating whenever possible how each of you as professional men are entitled to use and can actually use statistics even in the everyday routines of your profession.

Pediatricians can measure the growth of their profession by comparing the ten principal causes of death in 1900 with the ten leading causes of death in 1940 (Chart 1). Aided by clinical and laboratory researches which have developed drugs and methods for controlling many of the hazardous communicable and infectious diseases, members of the medical and related professions have seen diphtheria, diarrhea, and enteritis removed from the list of leading causes of death; have seen influenza-pneumonia and tuberculosis sharply losing rank positions in the list of principal causes of death, dropping from first and second positions in 1900 to ranks of 6 and 7, respectively, in 1940.

The statistics in Chart 1 are rates per 100,000 population which, as you know, are derived as follows: using the number of deaths from each cause for each year obtained from the death registration certificates in the rate formula:

$$\text{Death rate by cause} = \frac{\text{Deaths by cause}}{\text{Population}} \times 100,000$$

The population is the estimated July 1 population for 1900 and 1940, respectively. Bar charts are used, representing the independence of the causes of death. Attention has been given to the changing size of the Death Registration Area from 1900 to 1940 by the use of the original death registration states shown at the bottom of the chart.

Many of the rates used in subsequent illustrations are specific, that is, are limited to the deaths occurring in specific age groups of the population. Of course, the population base has been the number of children or persons in the respective or limited age groups for which the descriptions are given. The rheumatic fever death rate of 5.1 per 100,000 for children (from 5 to 9 years of age) is an age-specific death rate for rheumatic fever. Specific death rates are refined measures of the mortality risk which different segments of the population take. Some of the changes in leading causes of death from 1900 to 1940

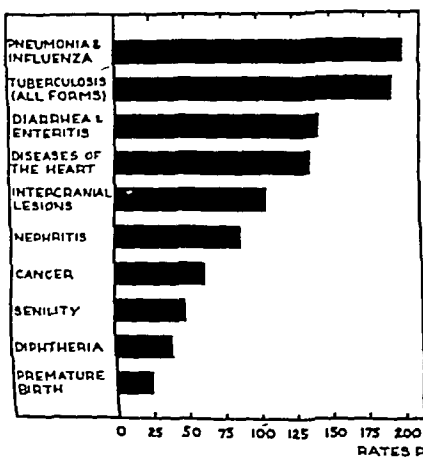
Presented before the Fourteenth Annual Meeting of the American Academy of Pediatrics, Detroit, Mich., Jan. 15-18, 1946.

LEADING CAUSES OF DEATH

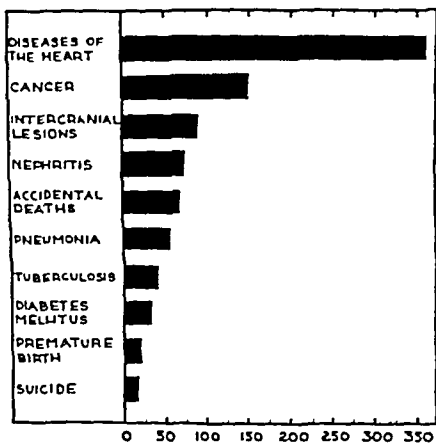
DEATH REGISTRATION STATES OF 1900*

IN 1900 AND 1940

1900



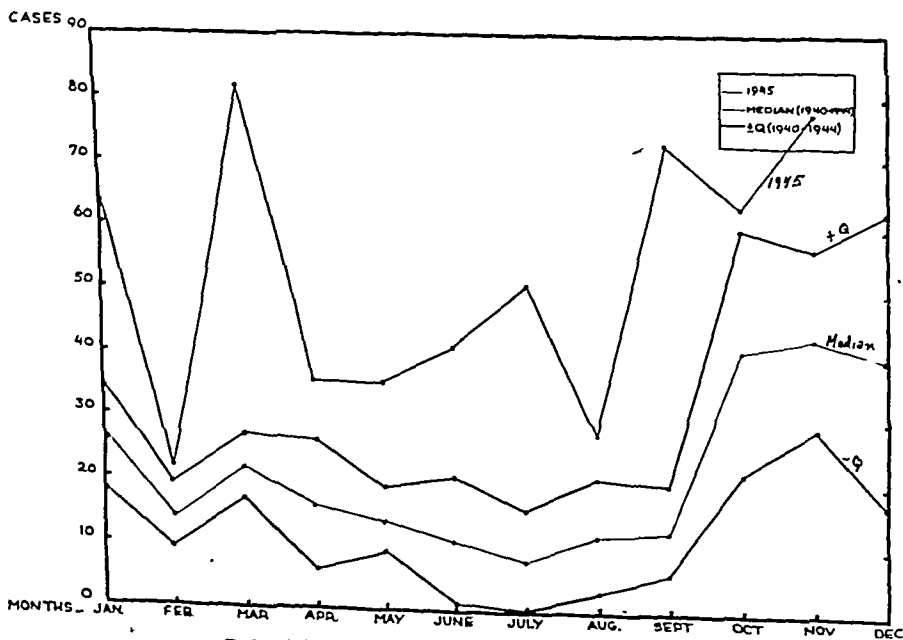
1940



*DEATH REGISTRATION STATES OF 1900—MAINE, NEW HAMPSHIRE, VERMONT, MASSACHUSETTS, RHODE ISLAND, CONNECTICUT, NEW YORK, NEW JERSEY, INDIANA, MICHIGAN.



Chart 1.



DIPHTHERIA IN MICHIGAN

(1940-1944) TREND AND 1945.

Chart 2.

not only measure progress in sanitation and preventive medicine, but also reflect the risks of an aging population.

Too often a favorable trend lulls a public and even a profession into complacency. The story of diphtheria in 1945, as told by the chart "Diphtheria in Michigan" (Chart 2) illustrates all too vividly this apathy. In 1945 diphtheria came to prominence through rapidly increasing numbers of cases, the increase exceeding the boundaries of expectancy definitely forecasting trouble. Members of the medical and public health professions have tried valiantly to arouse the trusting public to an awareness of the danger necessitating added protection such as is afforded by the booster dose given now to children who were immunized earlier in their life. Diphtheria can be controlled.

The statistics used to determine the boundaries for the diphtheria cases are relatively elementary. The line with the bands above and below, or average line, connects the median number of cases for each month over the five-year period 1940-1944. The January cases reported for each year of the five-year period are 40, 27, 26, 26, 25, respectively; thus giving a median of 26 cases for the average expected January incidence based on the five-year experience, 1940-1944. The $\pm Q$ boundary lines, those drawn equally distant above and below the median line, connect in succession the monthly quartile points, or the Q_1 and Q_3 points which for January are roughly at a distance of 7 cases on either side of the January median. This 7 is a crude expression of the January quartile deviation and has been found by the computation $\frac{40 - 25}{2}$. Just as the January quartile points were found, so have been derived the Q_1 and Q_3 values for each of the succeeding eleven months.

Since the cases reported in a given month in a given year are just a sample of the cases reported for the same month in other years, provided the diphtheria program continues under like conditions, the 1945 monthly incidence drawn as the top line should have fallen within the $\pm Q$ boundaries, that is, within the limits which chance fluctuations inherent in sampling would allow on a 50-50 basis. But at no month in 1945 has Michigan reported diphtheria cases within the boundaries set by the chance fluctuations inherent in sampling. The medical and related professions as well as the lay public can rightly be disturbed by diphtheria as it is occurring in Michigan in 1945. It is not chance that makes the 1945 top line fall so consistently above the expected incidence. Diphtheria in 1945 in Michigan is a real problem.

The prevalence of rheumatic fever in our young people is too often an unrecognized fact. Even the known fact that rheumatic fever mortality rises with age throughout childhood, having death rates of 5.1, 8.6, 9.3, and 10.2 per 100,000 children in successive five-year age groups beginning with the 5- to 9-year age group, is just beginning to arouse the public and to stimulate members of the medical and related professions to greater activity. Rheumatic fever is closely related to chronic rheumatic diseases of the heart and contributes to mortality from diseases of the heart (all forms). In 1940 deaths assigned to heart as cause accounted for 18 deaths in each 100,000 infants; took 4 lives out of each 100,000 preschool children; and increased the toll to 8 in each 100,000 school children.

Let us look at some of the diseases in the control of which you know that you have made progress—diseases which may or may not have ever appeared as principal causes of mortality in the total population but which are still definite hazards to childhood, to those age brackets of a population in which the pediatrician concentrates his efforts. Even though scarlet fever mortality dropped from nearly 10 deaths per 100,000 in 1900 to a mere $\frac{1}{2}$ death per 100,000 population in 1940, scarlet fever is still a hazard for the preschool child 1 to 4 years of age. Maximum scarlet fever mortality in 1940 occurred in this age group. Like scarlet fever, diphtheria in 1940 reached its peak mortality rate—9 deaths per 100,000—in the age group 1 to 4 years. Although more than 300 babies out of each 100,000 in 1900 lost their lives because of whooping cough, even in 1940, 100 babies in each 100,000 were being sacrificed to this cause. After 3 or 4 months of age the baby can be protected against pertussis.

Gross mortality in 1940 for tuberculosis of the respiratory system has been reduced to $\frac{1}{4}$ of the 1900 experience. But the pediatrician sees his charges die from tuberculosis: in 1940, out of each 100,000 children in their respective age groups, tuberculosis claimed 11 babies; 5 preschool children; 4 school children 5 to 14 years of age; and jumped up to 36 in the next ten-year bracket.

If dysentery deaths occur, expect them in the baby—51 deaths per 100,000 infants in 1940 were charged to this cause. But protect the preschool child also, for in 1940 seven out of 100,000 lives in this group were lost by this cause. But the diarrhea and enteritis story is more dramatic. In 1900 nearly 4,500 out of each 100,000 babies died from this cause; in 1940 this rate had dropped to a mere 400, serious enough to lose one baby in 250 to causes like diarrhea and enteritis. Even appendicitis, another cause falling in the category of digestive disturbances, claimed the lives of 7 to 8 children per 100,000 in 1940. In that same year 41 babies in each 100,000 died from intestinal obstructions.

All pediatricians recognize the risk of measles mortality which a baby incurs if he is unfortunate enough to have the exposure. Nine infants in each 100,000 died because of measles in 1940; more than one-fourth of all measles deaths in 1940 were contributed by the infants. Although the measles mortality rate was only 4 per 100,000 in the age group from 1 to 4 years, the preschool children accounted for nearly 50 per cent of all the measles deaths. When you think of an average of 400 cases of measles reported for each measles death registered, even in 1940 the pediatricians saw considerably large numbers of measles cases.

Closely linked with measles as sequelae are the respiratory diseases, such as bronchitis, influenza, and the pneumonias. In 1940 between 900 and 1,000 in each 100,000 children under 1 year lost their lives because of respiratory disturbances. Of the 70 deaths in each 100,000 children from 1 to 4 years of age, bronchopneumonia contributed 29; influenza, 14; and bronchitis caused 4 deaths.

Believe it or not, children do die from nephritis, an ailment commonly linked with the aging process. In 1940, 7 babies out of each 100,000 died as nephritis deaths; 4 preschool children in each 100,000 from 1 to 4 years of age, and 3 out of each 100,000 children from 5 to 14 years of age lost their lives because of nephritis. In that same year, syphilis accounted for the lives of 62 babies in each 100,000 infants—the age group having the maximum syphilis mortality.

The only age groups with death rates in 1940 exceeding 1 per 100,000 for mortality from cerebrospinal meningitis were those under 1 year, having a rate of 7, and those from 1 to 4 years of age, with nearly 2 deaths per 100,000. In 1940 the maximum poliomyelitis mortality occurred in the infant group which contributed a rate of slightly more than 2 deaths per 100,000. Children under 15 years contributed approximately 60 per cent of the total poliomyelitis deaths on record for 1940. With an average of 10 cases reported for each death registered, in 1940 there probably were nearly 6,000 recognized cases of this disease in children under 15 years of age. Poliomyelitis was an important problem for pediatricians in 1940.

If the pediatrician takes over the care of the baby from birth, then some of the facts and figures surrounding that birth are of interest to the profession. In 1940 nearly 30 per cent of infant deaths were charged to prematurity. If Wisconsin's 1944 experience—which is probably lower than the nation's average—of a 20 per cent case fatality rate for premature births holds, that is, if 1 baby dies out of each 5 who are born prematurely, then the obstetricians placed in your hands in 1940 more than 160,000 prematurely born babies.

I wish I knew how many congenitally malformed babies are born alive. True, nearly 85 per cent of all deaths charged to congenital malformations occur under 1 year of age; yet enough congenitally malformed babies live on to produce deaths from that handicap in every age of life—even in the 75 years and over bracket some congenitally malformed individuals failed to live longer because of their handicap. Not only are these individuals a medical problem, but also they become a very real social problem.

Perhaps similar comments might be made on injuries at birth. Some babies die as a result of injuries at birth at every age in the first year of life. It is conceivable that babies with injuries at birth survive past the infancy period to become both medical and social problems in later life.

So much for the infant who, if he has had proper postnatal care as well as prophylaxis against smallpox, diphtheria, pertussis, and possibly scarlet fever, reaches the preschool age as a relatively safe risk against mortality. Gross death rates are low for children from 1 to 4 years of age fluctuating around 3 per 1,000. But findings from the National Health Survey¹ indicated that the sample of preschool population surveyed showed 1 preschool child in every 4 had had some disabling illness during the twelve-month period covered by the Survey. This illness rate was lower than the 3 in 10 rate for the beginning school children from 5 to 9 years of age and higher than the illness rate of 153 in 1,000 for the children in the succeeding age bracket, 10 to 14 years. The length of the disabling illness for the 1- to 4-year age group was high but not as high as that for children from 5 to 9 years of age.

The illnesses which contributed to the 10 leading causes of death in 1940 of the children from 1 to 4 years of age and which are of concern to the pediatricians include: influenza and pneumonia; diarrhea and enteritis; tuberculosis; whooping cough; diphtheria; diseases of the ear, nose, and throat; and appendicitis. Gross mortality reaches its lowest rate, approximately 1 death in

each 1,000, in the age group, 5 to 14 years. The five leading causes which contributed to this low mortality rate were in 1940: accidents other than motor vehicle, followed by motor vehicle accidents, which account for the two principal causes, thus stressing the dangers of the increasing scope of activities engaged in by school-aged children; pneumonia and influenza; diseases of the heart; and appendicitis which emphasize the increasing risk to infection accompanying increasing contact with large numbers of people.

According to the National Health Survey¹ the highest rates for the disabling illnesses of childhood were those for the acute childhood communicable diseases: chickenpox, measles, and whooping cough; and for the acute respiratory infections. In surveys made in the eastern cities it was found that cardiac lesions, probably resulting from rheumatic fever, show an incidence as high as 4 in 100 children between 12 and 14 years of age. The toll from cardiac lesions begins to be felt in youth from 15 to 24 years of age, for whom deaths assigned to diseases of the heart take third place in the list of leading causes of mortality. At ages 5 to 24, death rates per 100,000 for rheumatic fever attain an average of 9 for girls and 8 for boys, and, with deaths from heart disease, account for nearly 15 per cent of all fatal diseases in young people.

Rejections for valvular heart disease, according to recent selective service statistics, reached a rate as high as 53 per 1,000 men examined. Nearly one-third of the rheumatic fever patients admitted to Philadelphia hospitals from 1930-1934 were between 5 and 10 years of age at first attack; New Haven Hospital and Dispensary records show the peak at 7 and 8 years of age for first attack. In the etiology of this disease it is important to note the relationship of the course of the incidence of this disease to the incidence of hemolytic streptococcal and other respiratory illnesses. It has been shown that crowding in homes is closely related to the incidence of this disease; that acute episodes reach a peak in spring. Clinical experience shows that a high per cent of deaths from heart disease for ages 5 to 24 can be attributed to rheumatic fever.

Much emphasis has been given to rheumatic fever in the hope that as pediatricians you will exercise control through early case findings and careful records and be stimulated to do some individual research: clinical, statistical, and epidemiological in the study of this baffling disease of youth.

Individual and group research is necessary for a profession, giving members an instrument not only for evaluating their own practice and for interpreting reported experiences of their colleagues but also for advancing the sum total of knowledge of the entire profession. The techniques in statistics offer powerful tools to research in any field.

The collecting of comparable, adequate, accurate and pertinent data is a prerequisite to any statistical analysis. A great deal of time and thought should be given to this phase of problem solving, because the end results or findings will never be any better than the original material on which the observations were made. In evaluating reported researches of your colleagues, you judge the findings not only by the integrity of the man through his established reputation, but also by the organs carrying the publications. In like manner you should recognize the inestimable value to yourself and colleagues of careful

personal study of the efficacy of the drugs advertised and circulated by the manufacturers of those products. True, most alert concerns accompany their advertisements by abstracts of researches showing the benefits of the use of the drugs. But you should be able to use some of the simplest statistical tools in order to be critical of reported results; and at the same time by watching results obtained in your use of the materials you can judge whether you can accept at their face value the findings of the efficacy of advertised products.

In other words you can always ask the questions: How good is this observation? How often can these results be found just by chance in material of the assumed composition? What can you expect to get as your results under like conditions; that is, what estimate can you make from the findings of the reported observation or sample?

Answers to these questions are found in the statistics of probability. A great deal of reliance can be placed on estimates even from small samples through the application of chance variation as given in statistics by what is known as tests for statistical significance. Time is limited, prohibiting a consideration of some of the basic principles in sampling and allowing an opportunity of presenting very briefly with illustrations only the most useful as well as simplest of these tests for statistical significance.

The probabilities or chances given in the interpretation of the use of the tests can be found in handbooks of probability tables such as: Areas under the normal probability curve; the X^2 and t tables of probabilities. The probabilities of the occurrence of chance in accordance with the Mendelian ratios are also available for combinations of successes and failures based on numbers of cases varying from $N = 1$ through $N = 50$. These tests are mandatory in any critical evaluation of results derived from small samples and should be applied to findings based even on large samples. Statistically a sample is usually considered small if it contains less than 50 cases and is certainly considered small if it contains 30 cases or less. The size of the sample is not necessarily indicative of a good sample. Small samples and large samples have value only when their contents are comparable. An experiment on 5 animals, comparable with respect to possession or absence of the factors known to be forces which condition outcome, is worth infinitely more than a large sample of 50 or more animals about whose comparability the experimenter has little or no knowledge at all. There is a value in comparability in small samples which often cannot be obtained in large samples. I am stressing here the critical selection of original source material.

In the use of any of the tests for statistical significance, please bear in mind that these tests, like your clinical tests, are designed for specific purposes and will do no more than what they are designed to do. Their use in no way can compensate for shoddy observations. Through their application, you, as well as the observer, can make allowance for chance fluctuations inherent in sampling, whether the samples are large or small. It is the privilege of the observer and a profession to set the confidence limits as standards of accuracy and safety. It is agreed generally by medical workers that in the field of chance and probability, an error of not more than 5 per cent should be allowed. In

other words, in subsequent illustrations interpretations of chance variations will be made at the 5 per cent level of significance, that level at which the observer is right 95 times in 100 and may be wrong 5 times in 100.

The statistical constants used in the discussion describe the p and q probability ratio where p is the probability of success or recovery and q is the probability of failure. The formulas are functions of the curve found by expanding the binomial $(p + q)^N$ and are the mean, which is $M = Np$ or Nq , depending on the approach made, recovery or death; the standard deviation or sigma, which is $\sigma = \pm \sqrt{Npq}$; the standard error of the mean which is $SE_M = \pm \frac{\sigma \text{ distribution}}{\sqrt{N}}$;

and the standard error of a rate or per cent, which is $SE\% = \pm \sqrt{\frac{pq}{N}}$. Sigma for a small sample has been found by using n instead of N . Small n designates independent items and is $N - 1$. This technique is important in the description of variability inherent in small samples.

The problems which follow have been selected on the criteria of interest to the pediatrician and the possible use which a professional man can make of knowledge gained in a presentation embodied in a single paper or talk.

The May, 1945, issue of the JOURNAL OF PEDIATRICS² carried an article on the use of a single dose of sodium sulfadiazine in meningococcic meningitis. The article was abstracted in *What's New*,³ a publication by the Abbott Laboratories as a service which this manufacturing concern is giving to the medical profession. According to the research, 8 out of 9 patients suffering from meningococcic meningitis received $2\frac{1}{2}$ grains of the drug per pound of body weight; one received only 2 grains. All of the patients in the group recovered.

The problem sets the question: How good is the 100 per cent recovery, based on the 8 patients receiving comparable doses of $2\frac{1}{2}$ grains? What could you expect to get as your recovery rate, supposing you treated your cases of meningococcic meningitis likewise by using a single large intravenous dose of sulfadiazine? Should you be disturbed if you observed only an 80 per cent recovery and not the 100 per cent reported in this research? In other words, what could an observed 100 per cent on 8 patients be expected to yield by chance under similar conditions in comparable samples? What are the boundaries for the "All or None" results reported on $N = 8$ patients? By expanding the binomial $(p + q)^8$ for various percentages of recovery, such as 90 per cent, 80 per cent, etc., it can be shown that an observation of 100 per cent recovery on 8 cases could be expected to yield recovery rates as low as somewhere between 65 per cent and 70 per cent at the 5 per cent level of significance. The true recovery rate 95 times in 100, based on an observation of a 100 per cent recovery on 8 cases, by chance alone can be expected to be anywhere between 65 per cent and 100 per cent but is unlikely to drop as low as 65 per cent. So if your experience under like conditions yields an 80 per cent recovery rate instead of the reported 100 per cent you need not be disturbed. The evidence even with the additional pressure of the 100 per cent or *all* indicates as unlikely a drop as low as 65 per

cent; but almost any recovery per cent between the boundaries of 65 per cent and the reported 100 per cent is possible. You would be missing your estimate only 5 times in 100. Tables are available which give the unlikely percentages for various numbers of items in a given sample when the observation on that sample yields a 100 per cent or the converse 0 per cent. Such a table gives the estimates of *true* percentages when samples show a 100 per cent or a zero percentage.

The same procedure with facilitating tables of probabilities can be used to evaluate percentages less than the "perfect" 100 per cent. In 1943 another article on meningococcic meningitis appeared in *War Medicine*⁴ with an abstract in *Therapeutic Notes*⁵ published by Parke, Davis and Company. Treatment with sulfadiazine or sulfadiazine and serotherapy on 39 patients resulted in only 2 deaths. The observed odds are 37 to 2. With the use of tables an observation of 37 recoveries out of 39 cases indicates true odds lying somewhere between 13 to 3 and 7 to 1. In other words you, as an observer administering the same treatment under like conditions can believe that the true recovery rate can be as good as 80 per cent or better.

If facilitating tables are not available for establishing true odds from observed odds, you can still evaluate how good an observed rate is by using the formula for the standard error, abbreviated S. E., of a rate. Let me illustrate with data from an article on the use of convalescent measles serum. The article appeared in a 1945 issue of the JOURNAL OF PEDIATRICS⁶ with an abstract in the July, 1945, issue of *Therapeutic Notes*.⁷ The serum was given intradermally in a daily dosage of 0.4 c.c. for five successive injections. Thirty-four of 38 children so treated did not develop measles. The observed escape rate is 90 per cent \pm 5 per cent. By the use of the \pm S. E. attachment, subsequent samples under like conditions may be expected to yield an escape rate as low as 80 per cent. The probability tables for odds would drop the expected escape rate at the 5 per cent level of significance to almost 75 per cent instead of the 80 per cent obtained by the use of the standard error test.

Another test, the "t" test, is used to evaluate how good is a mean or an average. Observations on blood sugar in 5 infants after twenty-four hours of fasting yield readings of 51, 69, 58, 60, and 63, respectively. The mean is 60.20 \pm 2.95. The evidence although based on only 5 cases is good enough to establish a highly statistically significant mean, since by chance fluctuations inherent in sampling, the variation which can be expected in the mean lies within the limits set by the 60.20 and the \pm 2.95 attachment. The t value which is the quotient of $60.20 \div 2.95$ is so large that the chances are considerably less than even 1 in 1,000 for an observer to be wrong when he expects a mean blood sugar content around 60.20 on infants observed under similar conditions, that is, after twenty-four hours of fasting.

The t test is useful in evaluating a mean change, such as is given by the observation of changes in serum protein with ammonium chloride and low sodium chloride diet made on 6 patients. The basic data are given in Table I.

TABLE I. CHANGES IN SERUM PROTEIN WITH AMMONIUM CHLORIDE AND LOW SODIUM CHLORIDE DIET

PATIENT	BEFORE	AFTER	CHANGE
1	6.12	6.57	+0.45
2	6.57	6.92	+0.35
3	7.44	7.93	+0.49
4	7.13	8.28	+1.15
5	5.85	7.47	+1.62
6	7.58	7.79	+0.21

The mean change is $.71 \pm .25$ which gives a t value equal to 2.84; for $n = 5$, a t value of 2.84 gives a P or probability between two and five times in 100 to be wrong, if on subsequent samples of similar observations, the observer expects an average change in serum protein within the limits set by the mean and its \pm sampling error attachment, that is, within $.71 \pm .25$. The evidence produces a statistically reliable mean.

Another test which is used frequently and which can be applied to both small and large samples is the X^2 or Chi Square test. Data for the illustration have been taken from the November 11, 1939, issue of the *Journal of the American Medical Association*⁸ and appear in Table II.

TABLE II. CHILDREN RECEIVING VIRUS BY OUTCOME OF VACCINAL CYCLE

VIRUS	VACCINAL CYCLE		TOTAL	PER CENT NOT ACCELERATED
	ACCELERATED	NOT ACCELERATED		
Culture	17	19	36	52.7 \pm 7.9
Calf lymph	29	5	34	14.7 \pm 8.1
Total	46	24	70	34.2

The uncorrected X^2 yields a value of 11.2. The corrected X^2 found from the computation

$$X^2 = \frac{\left[(29 \times 19 - 17 \times 5) - \frac{70}{2} \right]^2}{46 \times 24 \times 36 \times 34} = 9.6$$

The P or probability for a $X^2 = 9.6$ on $n = 1$ is much less than once in 100 times. The observer can expect that factors other than chance have influenced the difference in the accelerated cycles in the two groups using the two kinds of virus.

The uncorrected X^2 test value of 11.2 can be obtained through the use of the standard error test for statistical significance of a difference. The computation follows:

Culture virus	52.7% \pm 7.9%
Calf lymph virus	14.7% \pm 8.1%
Difference	38.0% \pm 11.3%

Critical ratio or C. R. = $\frac{38.0}{11.3} = 3.3$ sigma distances at which the observed difference is wiped out completely. From tables of areas under the normal probability curve, the P of occurrence beyond the 3.3 sigma distance is less than once in 1,000 times.

By both tests the professional man would be justified in ruling out chance as an explanation of the observed difference in percentages of acceleration or nonacceleration of vaccinal cycle as evidence in the use of culture virus versus calf lymph virus in smallpox vaccinations. There is much less than 1 chance in 100 for the observer to be wrong in his judgment in assuming an association between the type of virus and the involution of the vaccinal cycle to be due to chance alone. Some factor other than chance accounts for the observed result. It is the privilege of the professional man to accept or reject the evidence as indicative of the greater efficacy in the calf lymph virus in accelerating the vaccinal cycle.

Measurement in medicine is not new; but it is being emphasized through the increasing recognition given to the importance of its use in literature. In June, 1941, Campbell in *Surgery*⁹ considered statistical method a vital tool in clinical medicine. In a subsequent editorial on Campbell's article, the *Journal of the American Medical Association*¹⁰ stressed the point: that many clinicians still almost entirely neglect satisfactory criteria of statistical analysis in their scientific writings.

In a recent publication Stieglitz¹¹ recommends that "every periodical publishing material pertaining to health should have at least a professional medical editorial adviser and censor to ensure against the dissemination of misleading ideas; advertising services could greatly increase public confidence in advertised statements if physicians edited the claims of all food and drug advertisers."

I have tried to point out in this paper how statistics as numerically stated facts describe material of interest to pediatricians; I have tried to give a very elementary exposure of statistics as method, stressing specifically the rudimentary principles of the effects of chance, thus giving you some idea of what conclusions can be reasonably accepted from your own observation as well as those of your colleagues; what results you might expect if you were to repeat your own or the researches of others in your profession. Progress in medicine would be even more phenomenal than it has been in the last decade if ways and means were available to the large number of physicians practicing their profession relatively independently to pool their experiences; if these members had time and facilities afforded to them for evaluating the literature of their profession; and for critically accepting or rejecting the mass of materials affecting them and their public.

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STREPTOMYCIN: A SUMMARY OF CLINICAL AND EXPERIMENTAL OBSERVATIONS

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MOST pathogenic microorganisms do not long survive in the soil, even though they may survive elsewhere under similar conditions of temperature, food, and moisture. The death of pathogens in the soil is often rapid and due to identifiable chemical weapons produced by antagonistic microorganisms which are natural inhabitants of the soil. This concept, which has long been in the minds of such men as Waksman and DuBos, has led to the harnessing of this, another force of nature, for the welfare of mankind. It is difficult for us to imagine the evolution and survival of our race had the soil been a breeding place for contagion, as it once was thought to be.

Chemotherapy is one of the oldest fields of medical endeavor, but the chemotherapeutists of previous generations searched for remedies against disease by making extracts of higher plants. They were successful in discovering valuable and specific chemotherapeutic agents, including quinine and emetine, and such physiologically potent remedies as digitalis and opium. For the past two generations scientists have also been seeking antibiotic remedies from microorganisms in nature. The principles on which modern antibiotics were developed have been known for forty or fifty years and undoubtedly, if these principles had been persistently followed to their ultimate conclusion, penicillin might have been available a generation ago. We have been interested for several years in antibacterial substances which are effective against the bacillus of tuberculosis. By searching the available literature published during the last sixty years we have found references to at least twenty substances of microbial origin which showed some evidence of activity against the bacillus of tuberculosis. In many instances these are truly antibiotic substances as one thinks of them today.

Among the scores of antibiotic substances known, only two have as yet reached what appears to be a stage of practical development for the parenteral treatment of systemic human diseases. These are penicillin and streptomycin. It is the aim of this presentation to review briefly the information which has been accumulated regarding streptomycin during the two years since its announcement in January, 1944.¹

We have had the fortunate opportunity of studying streptomycin since April, 1944, when a small amount of the material was placed at our disposal by Dr. S. A. Waksman, having been produced in his own laboratory. This amount was adequate to treat only four tuberculous guinea pigs for a limited period, but the results² were sufficiently impressive to cause us to visit Dr. Waksman's laboratory immediately in order to discuss these findings and to plan for future

¹From the Division of Medicine, Mayo Clinic and the Division of Experimental Medicine, Mayo Foundation.

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studies on an adequate scale. The amount of material required for such experiments was beyond the productive capacity of Dr. Waksman's experimental laboratory, but with his help it was possible to enlist the aid of Merck and Company, who supplied streptomycin for earlier experimental problems. Since that time we, in collaboration with Drs. Herrell, Heilman, Nichols, Olsen, and others, have had the opportunity of utilizing between 5 and 6 kg. of streptomycin (5,000,000,000 to 6,000,000,000 S units*) in the treatment of experimental animals and in the treatment of more than 100 patients who had various infectious diseases.

Streptomycin has been found to possess most of the characteristics required of a successful antibacterial agent for the treatment of human disease. It possesses a range of antibacterial action in vitro not paralleled by any other available substance.^{3, 4} It may be administered by any of the usual parenteral routes conveniently. While streptomycin is rapidly excreted, the rate of excretion is somewhat less than in the case of penicillin and an adequate concentration may be readily maintained in the blood.^{5, 6, 7} Streptomycin maintains its activity in vivo and is active in the hydrogen ion concentration of the fluids and tissues of the human body. It appears to diffuse from the blood stream into most of the tissues.⁸ Streptomycin has an unusual property, which may give it some special clinical application, in that it is not absorbed to any significant degree from the gastrointestinal tract. Neither is it destroyed in the lumen of the bowel, but there it remains to exert an antibacterial effect on the intestinal flora, acting especially on the gram-negative bacteria which are normally so abundant in the colon⁹ and on several gram-negative pathogenic bacteria which inhabit the intestinal tract in cases of disease. Most important of all is the fact that streptomycin is of very low toxicity for man and the few unfavorable side reactions which have been observed^{7, 10} have been attributed to impurities. It now appears that the substance may be produced in commercially feasible quantities eventually and in a sufficiently high state of purity.

The antibacterial spectrum of streptomycin extends into fields of activity not covered by penicillin.^{1, 3} It should be clearly emphasized that streptomycin does not appear at this time to be in any sense a substitute for penicillin, but that its action is complementary to that of penicillin. Streptomycin possesses activity against many organisms which are relatively insensitive to penicillin, including a number of pathogenic, gram-negative, gram-positive, and acid-fast bacteria. While accurate predictions of therapeutic potentialities cannot be made on the basis of in vitro observations, experience indicates that antibiotic substances are more likely to retain their in vitro activity in vivo than are synthetic compounds, such as sulfonamides.

In studies on animals it has been found that streptomycin is active in vivo against experimental infections with penicillin-resistant microorganisms belonging to the genera *Salmonella*, *Pseudomonas*, *Shigella* and *Brucella*,¹¹ *Pasteurella*,¹² *Borrelia* and *Leptospira*,¹³ *Klebsiella*,¹⁴ and *Mycobacterium*.^{2, 15, 16}

*Supplied by Merck and Company, the Abbott Laboratories, the Upjohn Company, Eli Lilly Company, and Parke, Davis and Company.

The possibilities and limitations of streptomycin in treatment in human disease cannot be clearly seen at this time. However, it appears desirable to summarize the known facts which may be of value for guidance of physicians when streptomycin becomes more widely available in the near future than it is at present.

Until streptomycin is produced in greater quantity it should be used only in treatment of those patients for whom a definite bacteriologic diagnosis has been established. Furthermore, studies should be made to determine the actual sensitivity to streptomycin in vitro of the strain of pathogenic micro-organisms whenever these facilities are available. These recommendations are made to conserve the limited supply of the drug and to make results more intelligible than they would be otherwise.

Streptomycin is recommended for trial in treatment of infections of the urinary tract which have proved to be resistant to sulfonamides and penicillin and in which the infecting organism is susceptible to action of streptomycin. Infections which are due to *Proteus ammoniae* or *Aerobacter aerogenes* have responded best.¹⁷ If results are not promptly achieved in a few days with adequate treatment it is improbable that further treatment with streptomycin is indicated. The organisms frequently responsible for such infections may acquire drug fastness, especially if drainage of the urinary tract is defective or other conditions are favorable to reinfection.

Forms of bacteriemia due to organisms sensitive to streptomycin have been successfully treated.¹⁷ Such organisms may have had their origin from the urinary tract and these are frequently not sensitive to other available antibacterial agents.

The effect of streptomycin on brucellosis will require much more extensive study than has been given to it as yet. At this time it appears unwise to utilize streptomycin in treatment of chronic types of the disease or in those situations in which any doubt exists as to the validity of the diagnosis. *Brucella* bacteriemia has been treated successfully¹⁷ and in this circumstance it is possible to determine the sensitivity of the strain to the in vitro action of the drug.

Streptomycin has shown striking therapeutic benefit in treatment of human tularemia,¹⁸ a result which closely parallels that obtained in treatment of experimental tularemia.¹²

The possibilities of streptomycin in treatment of pulmonary suppurative disease have been under investigation by our colleague, Dr. A. M. Olsen, during the past year.¹⁹ Solutions of streptomycin may be readily nebulized and inhaled or solutions may be introduced supraglottically into the trachea. The drug may also be effective in suitable cases of chronic infections of the respiratory tract when administered intramuscularly.¹⁷ It has appeared that streptomycin should be used simultaneously with penicillin or following eradication of penicillin-sensitive microorganisms in most cases of pulmonary suppurative disease. Such applications of streptomycin require repeated bacteriologic examination of pulmonary secretion. The possibility of utilizing streptomycin in treatment of certain infections of the upper part of the respiratory tract, such as ozena, has been suggested by Herrell and Nichols.¹⁷ They also reported cases in which

peritonitis, cholangitis, typhoid fever, meningitis (due to *Hemophilus influenzae*) and syphilis were treated with streptomycin with variable results.

The first report of clinical use of streptomycin was that of Reimann and others²⁰ in treatment of typhoid fever. The medical profession will await with great interest further reports on parenteral and oral treatment of this disease with adequate doses of streptomycin because of the great prevalence of the disease in some countries and the lack of other specific remedies.

During the past six years we have made chemotherapy of experimental and clinical tuberculosis our principal research interest. Of the many substances tested in vivo in treatment of experimentally infected guinea pigs, streptomycin appears at this time to be the most promising. When guinea pigs received treatment continuously for about six months,¹⁵ lesions were found to regress in all instances. In 30 per cent of the animals no residual infection with tuberculosis could be detected by most careful histologic and bacteriologic methods and the tuberculin test gave negative results in these animals. The remaining 70 per cent of animals were free of evidences of progressive disease but residual lesions in various stages of healing were frequently demonstrated and tubercle bacilli could be isolated from emulsions of the spleen.

There are many contrasts between the pathologic changes produced in experimentally infected guinea pigs and those which occur in the many types of tuberculosis observed in man. Most important of all, however, is the fact that there are also many similarities and that the organisms responsible for human tuberculosis are extremely sensitive to the bacteriostatic action of streptomycin. We have previously expressed the belief that any effective bacteriostatic agent in clinical tuberculosis will have marked limitations dependent on the handicaps imposed by the pathologic characteristics of the disease.²¹ In a preliminary report¹⁰ we observed results consistent with the hypothesis that streptomycin exerts a "limited suppressive effect" on clinical tuberculosis. Further observations on these cases and on other cases in which treatment was subsequently given have yielded similar results and have served to support further our reservations as to the permanence of results in many instances.

In fifty-four cases of tuberculosis the patients have now received treatment with streptomycin under our direction for periods in excess of four weeks. In each instance the disease had shown progressive trends prior to institution of therapy. In twenty-one of these cases the patients had pulmonary tuberculosis and in sixteen cases the disease had attained a far-advanced stage of development. In every instance at least a portion of the tuberculous pulmonary infiltration was of known recent origin; hence these constitute a definitely selected group of patients with a less favorable prognosis than in average types of the disease. Roentgenographic and clinical evidence obtained during the period prior to treatment (control period) indicated to us that these patients possessed substandard resistance to tuberculosis. In no instance did the disease appear to extend into previously uninvolved pulmonary tissue while the patient was under streptomycin therapy and in at least sixteen of the twenty-one cases of pulmonary tuberculosis objective evidences of improvement appeared within four to eight weeks of institution of treatment. The rate of improve-

ent observed was frequently not greatly accelerated when compared with milar lesions among untreated patients with good resistance. It is suggested at these reparative processes are dependent on slow mechanisms of healing which cannot be stimulated artificially. No evidence of rapidly effective bactericidal action of streptomycin on the tubercle bacillus was noted but results were consistent with the hypothesis that the drug had a suppressive effect so long as its administration was continued. One patient in this series, who was in extremis when treatment was begun, died two months later despite roentgenographic evidence of slight improvement; this was the only fatality in the series.

Four patients who had generalized miliary tuberculosis in late stages have been treated and all have died despite unmistakable roentgenographic and histopathologic evidences of consistent healing trends. At necropsy the cause of death was not clearly evident on morphologic grounds.

Five persons who had draining sinuses of tuberculous origin have been treated. Closure of the sinuses has been observed in each instance but recurrences have developed in three cases after treatment was discontinued. A second course of treatment has been instituted and found to be apparently effective in two of these instances of recurrence.

Nine cases of renal tuberculosis have been observed. In eight the urine has been at least temporarily freed of tubercle bacilli, with definite improvement of symptoms. Cystoscopic observations have frequently shown evidence of healing of the tuberculous cystitis. Six instances of recurrent tuberculous bacilluria have already occurred after discontinuance of treatment and more are anticipated after lapse of further time.

Streptomycin has not shown a definite therapeutic effect on tuberculous pyemia when injected intrapleurally in five cases. This result is possibly due to unfavorable hydrogen ion concentration of the exudate or to other factors which are now under investigation in collaboration with Dr. Karl Pfuetze (Mineral Springs Sanatorium).

The remaining ten patients whose tuberculosis was treated with streptomycin presented miscellaneous manifestations of the disease, including some unusual types of extrapulmonary tuberculosis; in at least six cases there was objective evidence suggesting that a suppressive effect was exerted by streptomycin.

Much more study and observation will be required to define the possibilities and limitations of streptomycin therapy in cases of tuberculosis, but preliminary observations are sufficiently extensive and appear to be sufficiently encouraging to justify such investigative projects when supplies of the drug permit. In the meantime it is important to emphasize the limitations of streptomycin in treatment of tuberculosis, limitations which are at least in part due to the nature of the disease. We are fully cognizant of the danger of errors in clinical judgment of therapeutic effects in an unpredictable disease like tuberculosis, in which spontaneous healing frequently takes place. Such errors have been responsible for repeated waves of unwarranted optimism over other alleged remedies which ultimately failed. Streptomycin should not cause abandonment

or even postponement of methods of treatment of which the effectiveness has been proved. Such methods are care in a sanatorium and collapse therapy.

Streptomycin is being produced in small quantities only and as an experimental drug its distribution is regulated by Federal law. Manufacturers allocate supplies to special research projects and physicians engaged in such research are not permitted to divert supplies to other purposes. Until production is greatly increased, streptomycin will remain unobtainable even in many circumstances in which a trial of the drug would be clearly indicated.

CONCLUSIONS

Streptomycin possesses the pharmacologic characteristics required of a practicable antibacterial agent for treatment of human disease.

The range of efficacy of streptomycin extends the possibility of antibiotic therapy to treatment of several diseases which are not amenable to treatment with other chemotherapeutic agents.

Experimental tuberculosis of guinea pigs may be arrested by prolonged treatment with streptomycin even though the disease has been permitted to become well developed prior to institution of therapy.

A total of fifty-four patients with different types of clinical tuberculosis have been treated with streptomycin. The results indicate the necessity of much more extensive clinical use of the drug in treatment of tuberculosis on an experimental basis. Present evidence clearly indicates that streptomycin does not exert a rapidly curative effect on clinical tuberculosis, although it does appear to modify the course of the disease in a favorable manner and exert a suppressive effect on previously progressive tuberculosis. At the present time it must not be considered as a substitute for any other form of treatment.

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HISTOPLASMOSIS

A REPORT OF FOUR CASES, TWO IN SIBLINGS. HISTOPLASMIN TEST AND OTHER DIAGNOSTIC PROCEDURES

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INTRODUCTION

HISTOPLASMOSIS was first observed and described by Darling¹ in Panama in 1906. His three cases were in adults¹⁻³ and the first three cases reported from the continental United States were in persons above the age of 40. The observation of additional cases showed that the disease was not confined to the tropics nor did it occur only in adult life. In 1934, Dodd and Tompkins⁴ reported a case of this mycosis in a 6-month-old child living in Tennessee. The diagnosis was made during life and the fungus was first isolated in culture and identified by DeMonbreun.⁵ In the excellent summary review of the disease made by Parsons and Zarafonitis⁶ they point out that in eleven of sixty cases for which age data were available the patients were less than 1 year of age. Thereafter the frequency of histoplasmosis appears to drop sharply, rising again to a plateau in the age group ranging between 40 and 70 years. Histoplasmosis is of special interest to pediatricians not only because of its apparent predilection for infancy, but also because of the suggestion made by a number of investigators that this mycosis, fatal in nearly all recognized cases, may occur in a benign form which is now unrecognized and that therefore it may be much more common in childhood than is generally supposed. The apparent increase in the number of recognized cases may possibly be due to its more frequent recognition now than formerly, rather than an absolute increase in its frequency. However, some investigators believe that the actual incidence of the disease is definitely on the increase.

The following report represents a clinical summary of four cases of histoplasmosis which have been seen in Children's Hospital, Washington, D. C. Two of the cases, hitherto unreported, occurred in brothers and represent the first reported instance of histoplasmosis in siblings. The other two cases have been previously reported^{6,7} and will be reviewed briefly. These four cases are presented because they raise important epidemiologic considerations. All four patients were children living in Loudoun County, Va., within an area having a radius of eight miles, suggesting that there may be in this area an unusual geographical concentration of the mycosis (Fig. 1). In addition, the occurrence of histoplasmosis in siblings suggests that there may have been trans-

From The Children's Hospital and National Institute of Health.
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mission from one person to another. These circumstances will be considered in more detail after presentation of the case reports.

CASE 1.—S. D., a 7-year-old white male, was first admitted to the Children's Hospital, Washington, D. C., on Dec. 13, 1944, with the chief complaint of "swelling in the neck."

Approximately eight weeks before admission the child's mother noted bilateral enlargement of the glands in his neck. The gland in the right submaxillary region had caused the patient to complain occasionally of pain. His local physician was consulted for these glandular enlargements after they had been present for one week and sulfadiazine was prescribed, but no improvement was noted. During this time no fever had been present.

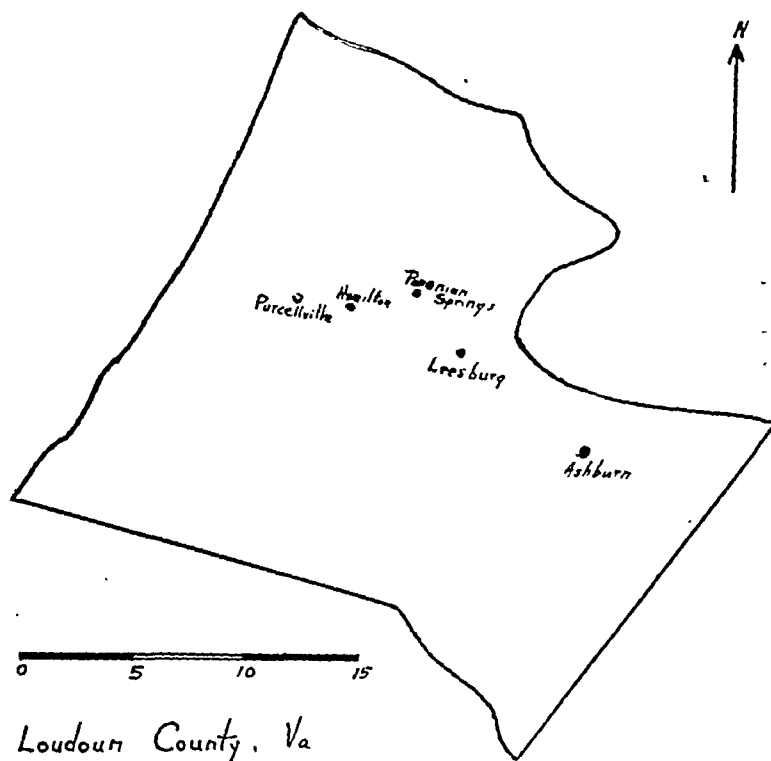


Fig. 1.—Loudoun County, Va., where the four cases of histoplasmosis occurred, illustrating their geographical proximity.

Four weeks later, the enlargement of the cervical glands persisting, blood specimens for agglutination tests were obtained and reported negative for typhoid, paratyphoid, tularemia, and brucellosis. The Weil-Felix reaction and a tuberculin patch test done at that time were also negative. The cervical glands, especially on the right, became progressively larger until his first admission on Dec. 13, 1944 (Fig. 2).

Past history revealed that approximately one year before, he had had an attack of "grippe" and shortly thereafter had an acute otitis media which spontaneously ruptured yielding a purulent exudate. He was unattended by a physician during this period. Eight months before his present illness he had made an uneventful recovery from chicken pox and about five months before had had a unilateral swelling in the parotid region which disappeared spontaneously after a few days. This was believed to have been an attack of mumps. The child visited the dentist about two years before his admission and was treated at that time for bleeding gums and whitish ulcers of the tongue and buccal mucosa diagnosed by the dentist as trench mouth,

The patient was born and raised in the town of Ashburn, Loudoun County, Va., and had lived there since birth, not having traveled beyond a radius of some twenty miles of Ashburn during his entire life. He was the second child; the first was premature and lived only one month. A younger brother, aged 5 years was the only living sibling and at that time was in good health. The patient's birth and developmental history were normal.



Fig. 2.—S. D. (Case 1) at the time of his first admission to Children's Hospital in December, 1944. Note the right-sided glandular enlargement in the neck.

The family drank a considerable quantity of bottled, pasteurized milk which was obtained from a farm in Ashburn. Until two years previously, the parents owned a cow and for several years the family drank raw unpasteurized milk from this animal. Water was obtained from a well which was stated to supply good water. The family kept chickens and two hogs. They had not permitted the boys to have a dog or other domestic pets.

Physical examination revealed a well-developed, well-nourished white male child who was not acutely ill or in any apparent distress. Lymph glands in the cervical and submaxillary regions were enlarged, particularly on the right side, the largest being about the size of a small hen's egg. The glands were quite discrete, freely movable, firm, and only slightly tender. Axillary lymph nodes were enlarged bilaterally and discrete. The inguinal nodes were palpable but not appreciably enlarged. The remainder of the physical examination was essentially negative.

A blood count revealed 11 Gm. hemoglobin, 3,300,000 red blood cells, 9,400 white blood cells, 55 per cent of which were neutrophils, 33 per cent lymphocytes, 7 per cent eosinophiles and 6 per cent monocytes. Blood culture and Wassermann were negative as was a stool examination for ova and parasites. Total serum protein was 8.53 Gm. per cent with an

albumin-globulin ratio of 1.1:1. A sample of blood taken for heterophile antibodies (Paul-Bunnell test) showed no agglutination in a dilution of 1:7.

On this first admission the patient showed a low-grade fever ranging between 99 and 100° F. during his five-day hospital stay. His weight was 55 pounds. A biopsy of a gland in the right side of the neck was taken on Dec. 13, 1944, and reported (Fig. 3) by Dr. J. W. Lindsay as follows: "Sections show a striking picture with numerous nodules of epithelioid cells, many of which are incorporated into large multinucleated giant cells of the Langhans-Schuffel type. In some areas there are broad pits of connective and reticulum tissue and in others dense masses of plasma cells. There is a border of somewhat hyperplastic lymphoid tissue and occasional eosinophile cells are noted. The condition is considered to be tuberculosis (or possibly Boeck's sarcoid) rather than neoplastic. The possibility of some fungus infection might be considered. It is assumed that the complement fixation test is negative."



Fig. 3.—Lymph node biopsy on Case 1 in December, 1944. The large multinucleated giant cells of the Langhans-Schuffel type are readily noted. ($\times 150$.)

X-rays of the hands and feet revealed no evidence of sarcoid deposits or any other abnormality and roentgenologic examination of the chest revealed only an increase in bronchovascular markings throughout the parenchyma but no other evidence of abnormality. A tuberculin skin test of $\frac{1}{10}$ mg. old tuberculin was negative. Five days after admission the patient was discharged to be followed at home.

A diagnostic course of x-ray therapy to the cervical glands was given anteriorly and posteriorly to the right side of the neck for four weeks. At the end of this time there was a rather remarkable reduction in the size of the glands although they never did actually disappear. Further roentgen therapy totaling 3,000 r was administered during the next five months to the various sites of glandular enlargement. The liver and spleen at the time of initial examination and during this follow-up period were never palpable although several times during this period the boy complained of a vague, recurrent, abdominal pain. In view of the clinical picture, the radiosensitivity of the cervical glands and failure to demonstrate any evidence of tuberculosis, the diagnosis of tuberculosis or Boeck's sarcoid, as suggested by the biopsy of the gland, was discarded and the probable diagnosis of Hodgkin's disease was favored.

During the ensuing ten months the patient ran a gradual downhill course becoming progressively weaker and a loss of eight pounds was noted during this period.

During July, 1945, the patient developed a severe diarrhea consisting of from four to six loose, bloody bowel movements a day. This diarrhea was accompanied by a lancinating type of pain in the lower center portion of his abdomen which was intermittent in character and seemed to have no relation to meals. His mother noted that his ankles began to swell shortly before his second admission in October, 1945. This edema was more prominent in the evening, disappearing during the night and usually being absent in the morning, but for the two weeks prior to the second admission this edema of the legs had been constant. During this observation period the patient's temperature had not been taken but the mother thought that he probably had some temperature elevation in the evening for two or three weeks prior to this second admission.

On Oct. 7, 1945, the patient was readmitted to the hospital because of progressive emaciation, persisting bloody diarrhea, and fever.

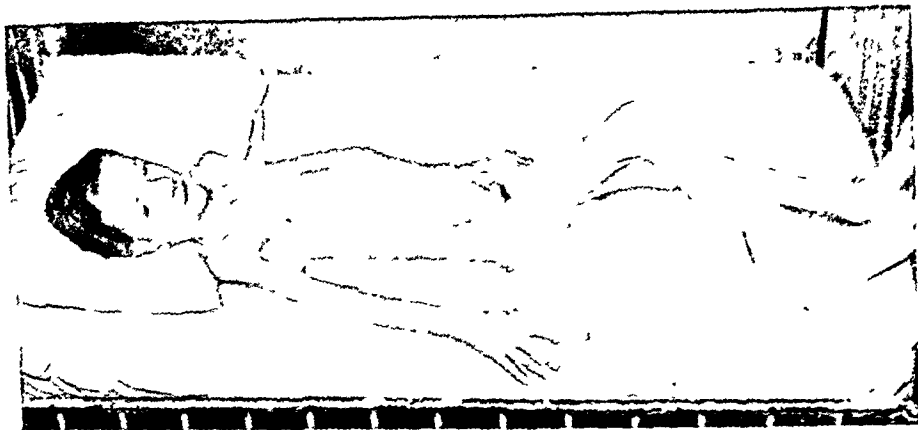


Fig. 4.—S. D. (Case 1) at the time of readmission to the hospital in October, 1945, illustrating the marked emaciation.

Physical examination upon this admission revealed a poorly nourished, markedly emaciated 7-year-old white male (Fig. 4) who was not in acute distress. The skin was dry and pallid. The anterior and posterior cervical, axillary, and inguinal glands were palpable, discrete, hard, nontender, and measured about 1 to 3 cm. in size. The pulse was 120, temperature 100.6° F. and respirations 22. The lips, gums, tongue, and mucous membrane of the buccal cavity were coated with a thick, whitish, curdlike crust, difficult to remove. The edges of the tongue were beefy red and were not coated. The heart and lungs were normal to percussion and auscultation. The abdomen was somewhat distended, but the liver and spleen were not palpable. There was no tenderness or rigidity noted. The extremities revealed a 2 plus pitting edema of the feet, ankles, and pretibial regions but were otherwise negative.

Roentgenologic examination of the chest showed a small amount of infiltration in the right base associated with some small areas of calcification at the roots of the lungs, which was interpreted as representative of a resolving bronchopneumonia. X-ray of the skull was negative. Examination of the blood revealed 7 Gm. of hemoglobin with 3,000,000 red blood cells. The white cell count was 4,600 with a differential count of 74 per cent neutrophils, 18 per cent lymphocytes, 5 per cent eosinophiles, 1 per cent basophiles and 2 per cent monocytes. Hemograms were repeated on four subsequent occasions and except for a variation in the hemoglobin and red blood cell count following blood transfusions, these remained essentially the same. Urinalyses were negative as were repeated blood and stool cultures. Agglutination tests were negative except for *Salmonella schottmülleri* which was positive in dilutions of 1:20 through 1:2,560. Three days later agglutination tests were repeated and again found positive in the same dilutions. Repeated examinations of the blood and stools, however, failed to demonstrate the presence of *S. schottmülleri*. The total serum protein upon this admission was 3.04 Gm. per cent with an albumin-globulin ratio of 1:2.1.

During the entire month of observation in the hospital on this second admission the patient continued to have a septic fever with the temperature fluctuating between 99 and 104° F. daily. The pulse followed the temperature and ranged between 50 and 130.

The patient was given a course of sulfadiazine for one week and after showing no response, this therapy was discontinued and for several days a trial course of penicillin was given, again without any effect. Treatment during this period was essentially symptomatic and consisted mainly of repeated blood transfusions and attempts to improve the nutritional status of the patient. This was followed by a disappearance of the edema of the legs.

A proctoscopic examination revealed marked hyperemia of the rectal mucosa with loss of the mucosal folds. The mucosa appeared edematous and brownish-gray but no ulcerations were observed. Bone marrow smear and culture were made and reported as showing no evidence of histoplasmosis; tuberculin skin test was repeated and again proved to be negative. A histoplasmin cutaneous test in dilutions of 1:1000, 1:100, 1:10 and undiluted were all negative in 24, 48, and 72 hours. All efforts to establish a diagnosis of histoplasmosis in this case were unsuccessful in spite of the fact that this diagnosis had already been confirmed in the case of his brother who had been admitted to the hospital on Sept. 28, 1945. (See Case 2.)

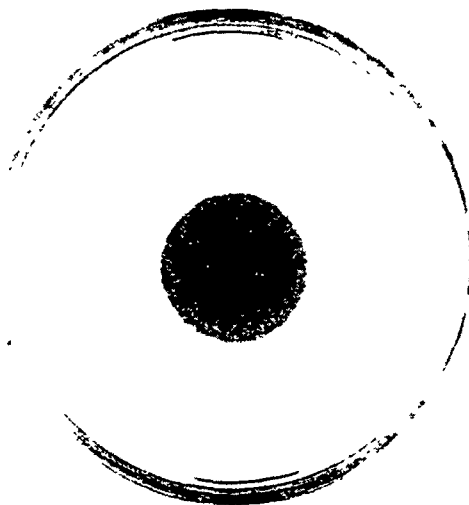


Fig. 5.—Illustrating the growth of *Histoplasma capsulatum* on Sabouraud's agar media.

Shortly after his brother died of histoplasmosis, the patient was discharged upon the request of his parents. The prognosis was obviously poor. At home, the child continued his rapid downhill course. He had lost a tremendous amount of weight and was extremely emaciated. At this time, examination and culture of the oral lesions and of stools revealed large numbers of *Candida albicans*. The severe bloody diarrhea had continued unabated at home and starting on November 16, he began to bleed from the rectum and died three days later on November 19.

A noteworthy feature was that almost concurrent with the patient's death, the bone marrow culture, which had been planted one month previously on Sabouraud's media, finally began to grow white fluffy colonies characteristic of *Histoplasma capsulatum* (Fig. 5).

Necropsy Summary.—Permission for examination of the head was not obtained. The body had been embalmed prior to the performance of the necropsy.

The liver extended 3 cm. below the costal margin in the mid-clavicular line. The surface was smooth and several grayish areas about 1 cm. in diameter were noted on the left lateral surface. On section the tissue had a distinctly yellow color and showed the nutmeg appearance of chronic passive congestion. No definite nodules or tubercles were found. Microscopically the parenchymal cells were found almost completely converted into fat. The few cells remaining more or less intact were swollen and pale staining. Numerous foci of leucocytic infiltration and degeneration or necrosis were seen chiefly in association with the vessels. Numerous *Histoplasma capsulatum* organisms were present.

The spleen was enlarged about one-third greater than its expected size and measured 11 by 9 cm. The cut surface was homogeneous and of a bright red color. Several gray areas averaging 2 mm. in diameter were noted. Microscopically, the spleen was found to be intensely congested. There were numerous foci of degeneration and necrosis with some areas of fibrosis. Several conglomerate tubercle-like formations were noted. The Malpighian corpuscles were rather less dense than usual. Many organisms having the morphology of *Histoplasma capsulatum* were noted.

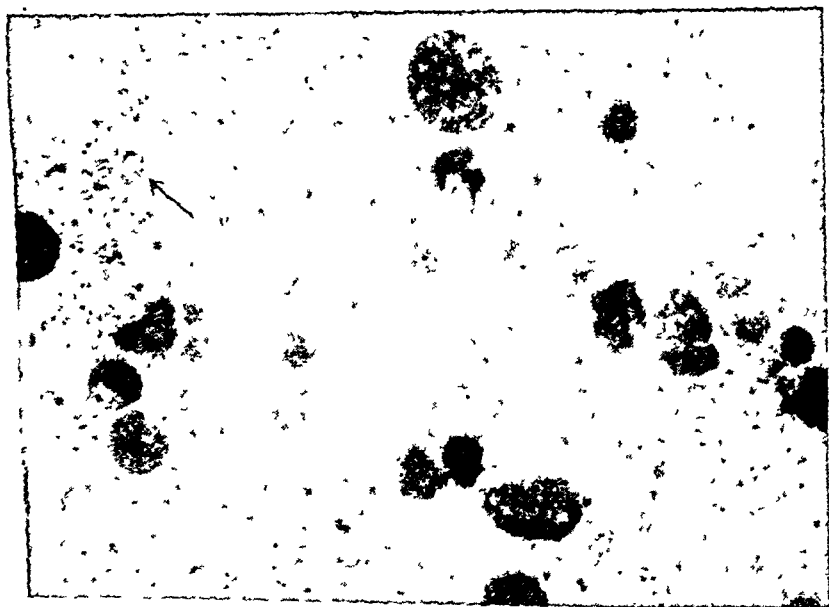


Fig. 6—Smear of bone marrow in Case 1. Arrow indicates a *Histoplasma capsulatum* organism. An estimate of the size of the organism can be obtained by comparison with adjacent red cells (X1350.)

The gall bladder, pancreas and adrenals showed no essential pathologic changes either grossly or microscopically.

On examination of the gastrointestinal tract the mucosa of the intestine was found to be hyperemic. Throughout the ileum were found areas of lymphoid hyperplasia more or less alternating with patches of ulceration. Other areas showed marked thickening up to 3 to 5 mm producing an annular constriction of the wall. On the serosal surface the sites of ulceration imparted a bluish color to the wall and it was evident that there was little more than serosa remaining of the entire wall in these areas. In the terminal ileum the lymphoid elements were hyperplastic producing a cauliflower like appearance. In the colon, areas of ulceration and thickening of the wall were also noted.

The cut surfaces of the kidneys were pale and edematous. At one pole of the left kidney a firm, gray, circular area, 5 mm. in diameter, having the appearance of a tubercle was noted. Histologically the kidneys appeared somewhat congested. The epithelial cells of the

convoluted tubules were somewhat swollen and granular while those of the straight tubules were hydropic and generally intact. Occasional foci of degeneration were noted. A moderate number of *Histoplasma* organisms were present.

Histologically the lung tissue was found to be generally air containing although there were scattered small areas of fibrosis. Many of the endothelial cells were filled with *Histoplasma capsulatum* organisms.

The retroperitoneal lymph nodes were found to be moderately enlarged and on section were found to contain numerous *Histoplasma* organisms.

The bone marrow was rather thinner than usual and on smear and culture revealed yeastlike bodies having the morphology of *Histoplasma capsulatum* (Fig. 6). Similarly a smear and culture of the spleen revealed these same organisms.

CASE 2.—J. D., a 6-year-old white male and the brother of the patient in Case 1, was admitted on Sept. 28, 1945, with the chief complaint of septic fever ranging between 100 and 104° F. since September 7. There were no other complaints except anorexia, loss of about 4 pounds and constipation. Prior to the onset of these symptoms, he had been in apparent good health.



Fig. 7.—Chest x-ray (Case 2) showing moderate infiltration more marked in the upper half of the right lung.

The family history and background were the same as in Case 1. The child had been in the same environment almost continuously with his brother, and except for a short hiatus, had slept in the same bed with his brother during the latter's prolonged chronic illness. His past history was essentially negative.

Physical examination revealed a pale, well-developed, well-nourished, 6-year-old white male, who did not appear acutely ill. The liver and spleen were enlarged 7 cm. below the costal margin, both organs being smooth, nontender and firm with sharply defined borders. The abdomen was protuberant but there was no ascites. The anterior and posterior cervical

lymph glands were slightly enlarged, discrete and nontender. There was some muscle atrophy due to disuse already evident in the extremities. Temperature upon admission was 100° F. and during his entire month's stay in the hospital prior to his death he showed a daily temperature rise ranging between 100 and 104° F. The pulse rate was rapid, ranging between 120 and 150.

Hemogram revealed a hemoglobin of 8.5 Gm. with 2,630,000 red blood cells. The white cell count was 8,400 with a differential of 71 per cent neutrophils, 26 per cent lymphocytes, and 3 per cent eosinophiles. Thrombocytes numbered 175,000 per cubic millimeter. Subsequent blood counts were essentially the same. A urinalysis was negative. Repeated agglutination tests with bacterial antigens were negative as were numerous blood cultures made on brain heart infusion media and blood agar pour plates.

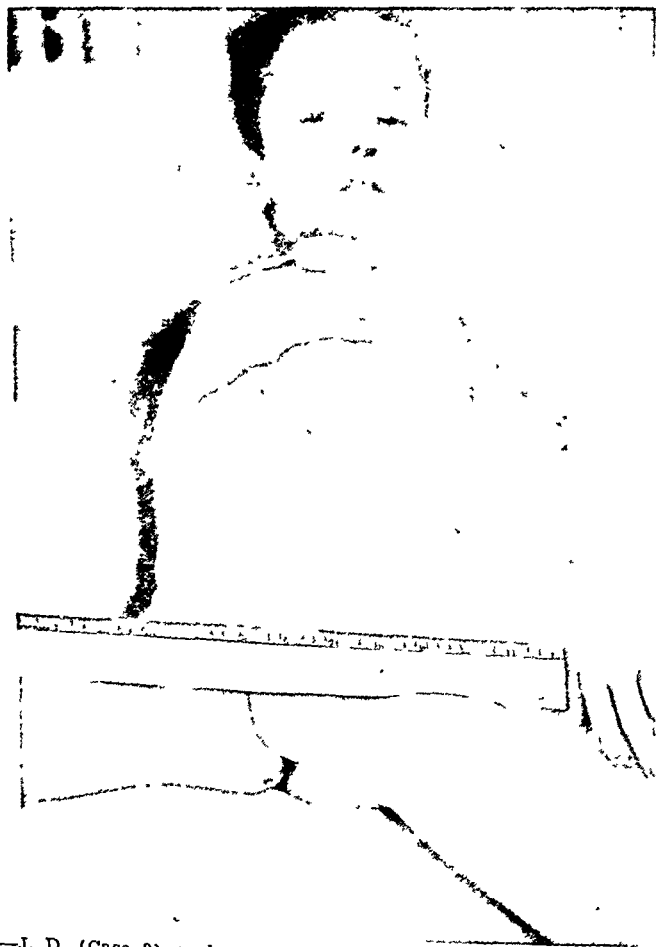


Fig. 8.—J. D. (Case 2) as he appeared about three weeks after hospital admission in October, 1945. At this time a diagnosis of histoplasmosis had been definitely established by sternal marrow examination. Note the delineation of the hepatosplenomegaly and the area of ulceration about the left nares and perineal region. The degree of emaciation is less marked than that of his brother (Case 1). (See Fig. 4.)

X ray examination of the chest revealed a moderate infiltration throughout both lungs extending from the apices to the bases, more marked in the upper half of the right lung and interpreted as representing bronchopneumonia (Fig. 7). X-rays of the long bones of the extremities were normal. An intradermal test for brucellosis was negative as were varying dilutions of tuberculin. The histoplasmin skin test in dilutions of 1:1000, 1:100, and 1:10 and undiluted were all negative.

The patient pursued a rapidly downhill course. The spleen enlarged rapidly almost to the iliac spine. He had several episodes of epistaxis and developed irritating ulcers in the region of the left nares and anus (Fig. 8). Sulfadiazine and penicillin were both given empirically without any effect.

A diagnosis of histoplasmosis or kala-azar was entertained following repeated negative attempts to establish a more common etiologic basis for the symptoms. Sternal marrow biopsy on September 19 definitely established the presence of numerous organisms having the morphological appearance of *Histoplasma capsulatum* (Fig. 9).

Therapy was entirely symptomatic as in Case 1. The patient expired on Oct. 27, 1945, one month after admission to the hospital.

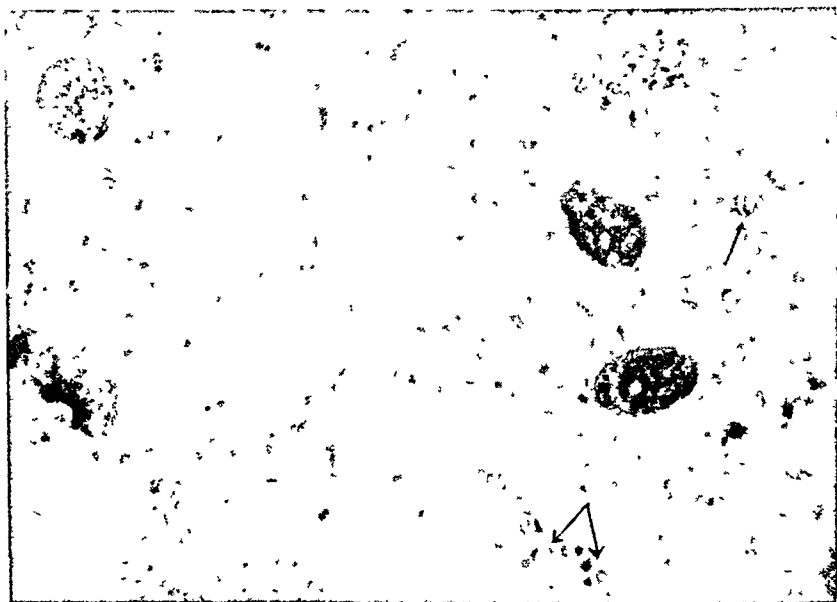


Fig. 9.—Premortem bone marrow smear of Case 2. Arrows indicate *Histoplasma capsulatum* organisms. ($\times 1350$.)

Necropsy Summary.—The body was that of a well developed, emaciated white male. There were fine capillary hemorrhages into the skin of the upper thorax and neck with a purplish mottling of the skin of the dependent portions of the body. There was some excoriation and ulceration about the left nostril. Two purpuric spots were present just below the anterior superior spine of the ilium.

Examination of the brain on removal and on section after formalin fixation revealed no evidence of pathology. The mediastinal and bronchial lymph nodes were gray, firm, and markedly enlarged. They formed a collar about the trachea and were prominent in the hilar regions.

Approximately 30 c.c. of turbid orange colored fluid was present in each pleural cavity. On examination of the lungs the surfaces were found to be smooth with color varying from a bright red to dusky maroon. They were quite firm and, while definitely congested, they had a more homogeneous appearance on section than could be accounted for from edema and congestion alone. The cut surface showed a number of gray nodules measuring several millimeters in diameter scattered throughout the parenchyma. On microscopic examination there were broad, densely consolidated areas apparently due to atelectasis with pneumonitis. Plasma and endothelial wandering cells appeared to predominate. Many of the endothelial cells were filled with *Histoplasma* organisms.

The pericardial sac contained about 20 c.c. of deep yellow clear fluid. The heart weighed 150 grams (normal 94 grams). On the surface of the right auricle just above the inferior vena cava, a 3 mm. yellow nodule was found which extended a short distance into the muscle wall.

The peritoneal cavity was found to contain about 50 c.c. of clear, straw colored fluid. On examination of the liver the external surface was found to be smooth and light brown in color with innumerable yellowish-white flat areas varying in size from 1 to 6 mm. in diameter scattered over the surface. The cut tissue was reddish brown with many grayish miliary areas scattered throughout. On microscopic examination the parenchymal cells were well preserved. There were numerous areas of degeneration or necrosis and some fibrosis in these areas. Great numbers of *Histoplasma* organisms were found frequently filling the cells.

The spleen was considerably enlarged weighing 660 grams (normal 50 grams). The surface was relatively smooth, of a dark maroon color with many round gray areas scattered throughout. The largest grayish-white area measured 5 mm. in diameter. On microscopic section the spleen was found to be considerably congested and there were many *Histoplasma* organisms noted.

On examination of the gastrointestinal tract, the ileum and cecum were found to contain a number of firm, yellowish-gray, elevated masses extending from the mucosa. Occasionally some ulceration was observed. The Peyer's patches were prominent and were apparently undergoing ulceration. The pancreas, the adrenals, and gall bladder were essentially normal.

The surface of the kidneys was smooth and light grayish rose in color with many firm, red, interlacing lines due to capillary engorgement. The cut surface was smooth and reddish gray with poor differentiation. On histological examination there was striking granular degeneration and swelling of the epithelial cells. The glomeruli were congested and there was some degeneration of the capillary cells. The *Histoplasma* organisms were only sparsely scattered through the kidney tissue.

The ureters, bladder, and generative organs were normal. The celiac, retropyloric, pre pancreatic, and mesenteric lymph nodes were markedly enlarged and firm.

Histoplasma capsulatum was isolated in culture from heart's blood, spleen, and liver.

CASE 3 (Previously reported by Shaffer and associates⁷).—F. C., an 11-month-old white female, was admitted to Children's Hospital on July 22, 1938, with a chief complaint of inter-

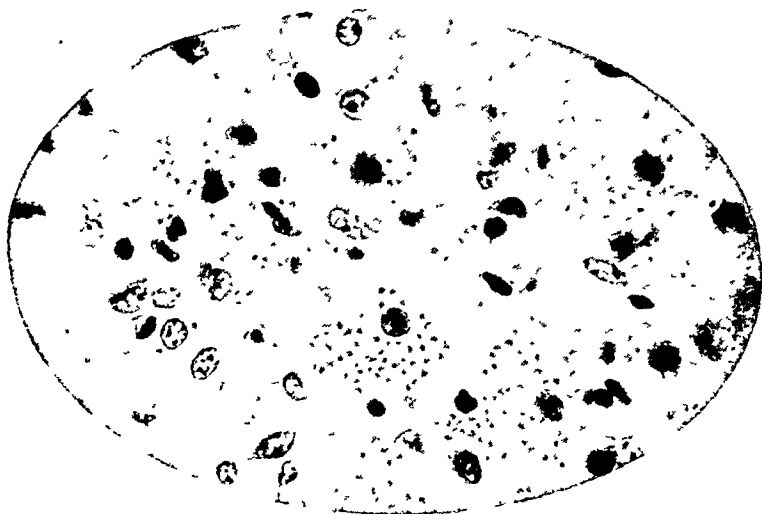


Fig 10—Adrenal gland in Case 3 showing numerous *Histoplasma capsulatum* organisms.

mittent fever of four months' duration. One month prior to entry, the infant exhibited a marked drowsiness accompanied by periods of alternating diarrhea and constipation.

Past history and family history were noncontributory. The patient lived on a farm near Paeonian Springs in Loudoun County, Va., approximately 15 miles from the home of the two previously described patients.

Physical examination revealed bilateral cervical adenopathy and marked hepatosplenomegaly. Temperature was 103° F.

Laboratory examination showed a severe hypochromic anemia, and leucopenia with a shift to the left of the white cell series. A platelet count revealed no thrombocytes on smear. Urinalysis was negative. Tuberculin, Schick, Wassermann, and Kahn tests were all negative. Sternal puncture was attempted without success on August 5, eight days before death.

In view of the presence of hepatosplenomegaly and the aberrant blood picture, a clinical diagnosis of aleucemic leucemia was entertained.

The patient's course in the hospital showed a rapid terminal progression. The temperature fluctuated between 100 and 105° F. during the entire hospital stay. Shortly before death, a small gangrenous, pea-sized area of ulceration appeared on the right ala nasi and became progressively larger. The patient died on August 12, approximately seven months after the onset of illness.

On post-mortem examination, organisms having the morphology of *Histoplasma capsulatum* were found in almost all tissues including the liver, lungs, spleen, mesenteric lymph nodes, kidneys, adrenals, bone marrow, and subcutaneous tissue (Fig. 10).

CASE 4 [Parsons and Zarafonitis—Case 61 (Hunter)].—C. S., a 4-year-old white female, was admitted to Children's Hospital under the care of Dr. Edgar P. Copeland in October, 1922, with a chief complaint of intermittent fever and progressive loss of weight. In March, 1921, eighteen months prior to entry, she began to run an intermittent fever accompanied by marked lethargy and loss of appetite. This episode continued for about three weeks, following which she showed marked improvement and, according to the parents, regained her normal health. During the next eight months the child appeared moderately well except for periodic episodes of high fever and prostration which continued for one or two days and then subsided. In the intervals between these sporadic exacerbations of fever she appeared moderately alert and active.

Six months prior to entry, she began to lose weight steadily and appeared quite listless. At this time she was admitted to another hospital and was discharged two weeks later, ostensibly improved. No diagnosis was made at this time.

During the next six months her fever continued in intermittent fashion. She became progressively more emaciated and during this time her abdomen was noted to have become enlarged. About four months prior to entry "walnut-sized boils" appeared on her scalp and recurred in crops at various times subsequently. *

The past history and family history were noncontributory. The patient was residing in Hamilton, Va., in Loudoun County at the time of the onset of her illness. This locality is not more than ten miles distant from the homes of the other patients (Cases 1, 2, and 3).

She was admitted to Children's Hospital on August, 1922. Physical examination on entry revealed a severely emaciated 4-year-old white female who appeared chronically ill. Respirations were rapid and shallow. There were numerous furuncles on the scalp. The cervical, axillary, and inguinal nodes were enlarged as was the liver and spleen. The physical examination was otherwise negative.

During her course in the hospital she became progressively worse. The temperature remained persistently elevated during her entire stay and the child expired one month after entry.

On post-mortem examination, histological examination revealed parasitic organisms which, at the time, were thought to be Leishman-Donovan bodies and a diagnosis of kala-azar was made. However, a review of these microscopic sections recently by Dr. Oscar Hunter and the pathologists at the Army Medical Museum, Washington, D. C., suggested that these organisms were *Histoplasma capsulatum* rather than Leishman-Donovan bodies.

DISCUSSION

Pathology.—*Histoplasma capsulatum* grows as a small, yeastlike organism in the reticuloendothelial cells, tissue endothelial cells, and the blood and marrow mononuclear cells. Humphrey⁸ has described three rather well-defined types of lesions in histoplasmosis. In the first stage "there are areas in which isolated phagocytic cells are filled with parasites," followed by a second phase in which necrosis occurs in the area involved and in the third phase, which is the result of necrosis, "fibrous tissue and hyaline masses replace the lesion and scarcely any laden phagocytes remain." Any of these three stages can exist simultaneously in the same patient although one of three phases may dominate the picture.

Histoplasmosis is usually a generalized disease, although on occasions, localized lesions may occur in the absence of generalized involvement. In a case reported by Phelps and Mallory,⁹ the presenting symptoms were confined to the respiratory system and post-mortem examination revealed only pulmonary infection.

At autopsy, hepatosplenomegaly and lymphadenopathy are frequently noted with histological examination revealing a phagocytosis of the fungi by the reticuloendothelial cells and the intracellular multiplication of the organisms. In fifty-six autopsies summarized by Parsons,⁶ lymph node involvement was found in thirty-seven. As was noted in the necropsy summary of the cases reported here, the presence of tubercles in the liver, the spleen, kidneys, and lungs also was a frequent finding. Ulcerated lesions of the gastrointestinal tract were also a prominent feature in these cases. The lungs were very frequently involved especially in cases of generalized histoplasmosis; Parsons noted the occurrence of pulmonary lesions in thirty-four of sixty-one cases. The adrenals were involved in about one-third of the cases. Other organs involved with varying frequency are bone marrow, kidney, skin, buccal cavity, larynx, pancreas, ear, brain. In three cases, vegetative endocarditis was noted.

Diagnosis.—

Clinical Diagnosis: In Darling's 'original report,' he described the disease as being characterized by splenomegaly, emaciation, and prolonged intermittent fever. Subsequent case reports have shown considerable variation in the symptomatology and the physical findings. In their comprehensive summary report, Parsons and Zarafonitis⁶ found an irregular temperature to be an almost constant feature, although normal temperature in rare cases may be present during periods of remission. Anemia, hepatomegaly, splenomegaly, and lymphadenopathy were present in a majority of cases reviewed by Parsons while leucopenia, gastrointestinal symptomatology, emaciation, and ulcerations of the mouth and buccal cavity were present in approximately one-third to one-half of the patients.

The inconsistency of the presenting symptoms and the fact that it simulates several other disease entities makes the clinical diagnosis of histoplasmosis relatively impossible. In cases of hepatosplenomegaly with depression of the formed elements of the blood, the disease may readily be confused with aleucemic leucemia. In Case 3 of the series reported here, this latter diagnosis was enter-

tained premortem. Similarly the presence of marked lymphadenopathy may simulate Hodgkin's disease, lymphosarcoma and tuberculous adenitis. In a case seen by Drs. Paul Steiner and Paul Cannon and reported by Parsons and Zarafonetic⁹ Hodgkin's disease and histoplasmosis were found to coexist. In one of the cases reported here (Case 1), the diagnosis of Hodgkin's disease was seriously considered in view of the marked lymphadenopathy on entry and this impression was enhanced by the rapid disappearance of the nodes under roentgen therapy. However, a biopsy of one of the nodes premortem failed to reveal the presence of Reed-Sternberg cells. In this regard Parsons and Zarafonetic⁹ poses the question of whether "Hodgkin's disease, a disease in which cells of the reticulo-endothelial system become malignant, predisposes to histoplasmosis, a disease characterized by parasitization of the cells of the reticulo-endothelial system by the yeast-like forms of the fungus *Histoplasma capsulatum*." Kala-azar may also present difficulty in the differential diagnosis because of the close resemblance of the Leishman-Donovan bodies to *Histoplasma capsulatum*. However, as Crumrine and Kessel¹⁰ have pointed out, the cell wall of *Histoplasma* is much thicker than the wall of *Leishmania* and the structure and irregular area of chromatin material within the cytoplasm are more suggestive of a fungus cell than a protozoan cell. Moreover, *Histoplasma* buds in the manner of a yeast.

In view of the chronicity, the intermittent fever, the leucopenia and anemia which are usually present in histoplasmosis, this disease may simulate brucellosis, malaria and infectious mononucleosis. The disease must also be distinguished from syphilis, neoplasm, tuberculosis, and other fungus infections in the presence of cutaneous and oropharyngeal lesions. Histoplasmosis must also be differentiated from bacillary and amoebic dysentery, tuberculous enteritis, and more rarely from idiopathic ulcerated colitis in cases where intestinal ulceration and diarrhea are prominent features of the disease. In the first case of our series, severe diarrhea persisted for several months prior to death; this may have been due to histoplasmosis or possibly a superimposed paratyphoid infection as suggested by the agglutination titer of 1:2,560 for *S. schottmülleri*.

Laboratory Diagnosis: The diagnosis of histoplasmosis can be established only by the laboratory demonstration of the fungus. The study of the blood smears and cultures and aspiration of bone marrow have been said to afford the most successful method of making the diagnosis. However, Parsons points out in his review of seventy-one reported cases that, in the nine cases where bone marrow aspiration was performed, the organisms were demonstrated in only five cases while the other four cases failed to show the parasites. It is interesting to note that three of the five cases in which this method of diagnosis was successful occurred in infants. However, as for finding the organism in blood smears, this was accomplished in only four cases. The conclusion seems rather warranted that examination of the blood smears is not too reliable a diagnostic criterion since the fungus is present in the circulating blood only intermittently, or only in very small numbers or only terminally. In two of the cases

reported here the organisms were demonstrable on bone marrow examination both premortem and post mortem.

Repeated premortem blood cultures planted in blood agar pour plates and brain-heart infusion broth were consistently negative in both Cases 1 and 2. This may have been due to the fact that cultures on blood agar pour plates were considered negative when no growth had appeared after five days. In this regard, Beamer and associates¹¹ have found that blood cultures may reveal growth as early as the third or fourth day following inoculation of the media. However, Parsons emphasizes the necessity of observing the blood cultures of histoplasmosis for at least two to three weeks before discarding them as negative in view of the slow growth of the organisms; positive blood cultures were obtained in nine instances in this author's summary of the seventy-one reported cases.

Biopsy of lymph nodes, spleen, and material from ulcerations probably constitutes the most reliable method of making the diagnosis. In Case 1 of our series a biopsy of the lymph nodes failed to show the organisms, however.

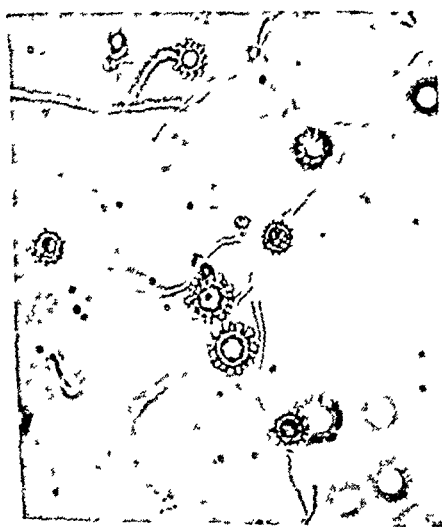


Fig 11—Chlamydozooids of *Histoplasma capsulatum* from a culture

Examination of the stools for the presence of *Histoplasma capsulatum* is emphasized by Henderson and associates¹² in view of the frequent intestinal involvement. Similarly, there is some suggestive evidence that the organism may be cultured from the urine, with the demonstration by Reid and associates¹³ that positive urine cultures could be obtained from the urine of guinea pigs after these animals had been infected by the intravenous administration of *Histoplasma capsulatum*.

The organisms can usually be stained effectively with Wright's, Goodpasture's, Masson's trichrome, and Giemsa stains. The fungi are found as budding yeastlike cells in the cytoplasm of monocytes and polymorphonuclear cells, and in heavy infestation, many will be found free following rupture of the parasitized cells. Depending upon the extent to which the fungus has multiplied within the host cell it may occur singly or in such great numbers that

the host cell is filled. These fungus cells vary in size but are usually 2 to 3 by 3 to 4 microns. Budding can be observed in many of them. The fungus is egg-shaped like a true yeast and the bud is usually attached near the smaller end of the cell. Presumably each cell is capable of budding repeatedly in this region but as a rule only one bud is seen attached at any time. The bud may reach nearly the size of the parent cell before it is displaced. When viewed in tissue sections, there may appear to be a greater variation in the shape and size of the fungi because more of them are oriented in such a way as to be seen in cross section whereas in smears most are in longitudinal sections.

In a Giemsa stained smear certain differentiated internal structures may be observed in the fungus cell. There is a mass of purplish staining material which is usually located near the base of the cell although during the process of budding it may be located next to the bud and similar material may be seen in the bud. If the bud is young or partially formed, these chromatin masses may be continuous from parent cell to bud, but in the older buds, the chromatin has migrated to the distal end of the bud and the parent chromatin mass has returned to the base of the parent cell. Under some conditions this mass is cup-shaped. This undoubtedly represents the nucleus of the cell which divides during the process of budding, but the actual structure of the nucleus is not well preserved by the ordinary techniques of staining. In addition to the chromatin, the cell also contains blue staining cytoplasm and usually a small centrally located vacuole can be seen.

While the appearance of *Histoplasma* in smears and tissue sections and its relationship to phagocytic cells is sufficiently characteristic to differentiate it from most other known pathogenic fungi, it is necessary to isolate it in cultures to positively identify it. When the fungus is present in the circulating blood, this is comparatively easy. About 0.5 c.c. of venous blood is placed on the surface of an agar slant. Cultures can be made on blood agar slants which are then sealed and incubated at 37.5° C. to obtain the yeastlike form of the fungus in culture, or they can be made on any ordinary agar such as Sabouraud's and incubated at room temperature or 30° C. to obtain the mold growth phase. The fungus may be isolated from an excised lymph node by planting the material in the same manner. It can also be isolated from ulcers and sputum, but the bacteria present make this a slow and uncertain procedure.

On blood agar incubated at 37.5° C. some strains of *Histoplasma* grow in the budding yeastlike forms seen in tissues. There may be multiple budding and short chains of yeastlike cells and abortive hyphae are frequently seen, that is, this growth is intermediate between the parasitic and saprophytic stages. On agar at room temperature, it produces a white mold which becomes brown with age. Spherical spores 2 to 4 microns in diameter are formed on slender stalks arising from the mycelium. Characteristic spores are 6 to 15 microns in diameter, thick walled and bear fingerlike projections radiating from the wall. The thick wall imparts a yellow color to the spores. Many small food granules which take the fat stains are present in young spores and these fuse into a few or into a single large hyaline mass in most old spores. The peculiar radiating

adornment of the spores may be slender and almost spiny, fingerlike or fused into large obtuse masses. They appear to be derived from some material which exudes through the cell wall. When spores from this saprophytic growth phase are injected into a laboratory animal, the fungus at once reverts to the yeastlike form.

Parsons and Zarafonetis⁶ recommend the use of experimental animals in the isolation of *Histoplasma* from contaminated material. They inoculated young mice intravenously with suspensions of ground lymph nodes from one case. All mice became infected. Dr. Carl L. Larson of the National Institute of Health isolated *Histoplasma* from contaminated material from Case 2 of this report by the intraperitoneal inoculation of mice. Parsons has described in detail the progress of experimental histoplasmosis in mice. Other susceptible animals include guinea pigs, rats, rabbits, dogs, and chick embryos.

We have found the hamster an excellent experimental animal. It seems to be somewhat more susceptible to histoplasmosis than the white mouse and experimentally infected animals died from two to four weeks following inoculation depending upon the dose given. A laboratory strain of *Histoplasma* has been carried serially for several generations in this animal using ground spleen, liver, or peritoneal fluid for animal passage.

Significance of the Histoplasmin Skin Test.—The desirability of having a specific cutaneous test to detect histoplasmosis is apparent since it would not only aid in diagnosis, but would also detect healed or arrested infections. Van Pernis, Benson, and Holinger¹⁴ and Zarafonetis and Lindberg¹⁵ developed a histoplasmin skin test which could be given intradermally to produce an erythema and induration at the site of infection. Emmons and associates¹⁶ reported that 0.1 c.c. of a dilution of 1:100 of histoplasmin, prepared by growing *Histoplasma capsulatum* from two to seven months on the synthetic broth used in making tuberculin, gave a positive reaction in guinea pigs inoculated experimentally with *Histoplasma*; this reaction occurred within twenty-four to forty-eight hours and an arbitrary standard of positivity consisted of an area of edema .5 cm. or more in diameter after intradermal injection. These authors point out that in positive reactions, the area of erythema usually corresponds to the area of induration.

Palmer,¹⁷ investigating the possibility that an infection with *Histoplasma capsulatum* is the cause of nontuberculous pulmonary calcification, found that among 3,105 nurses studied in the eastern and midwestern United States, 711 (22.9 per cent) showed positive skin reaction to histoplasmin. The percentage varied from 6.3 per cent in Minneapolis, Minn., to 65.8 per cent in Kansas City, Mo. Among the total group, 294 showed areas of primary calcification on x-ray and of this number with calcification, approximately four-fifths had a negative tuberculin test. Rather striking was the fact that 70 per cent of this group showed positive or doubtful histoplasmin tests. From these studies, Palmer concludes that histoplasmosis, or an immunologically related fungus, may account for the presence of pulmonary calcification in tuberculin negative reactors. A corollary of this would be the fact that histoplasmosis in a benign self-limited form may be quite prevalent, at least in the central and eastern half of the United States.

The correctness of this conclusion would rest on the specificity of the histoplasmin used in skin testing. Emmons, Olson, and Eldridge¹⁶ have demonstrated, however, that the histoplasmin is not specific in histoplasmosis but shows cross reactions with blastomycosis, coccidiomycosis, and haplomyces and these authors conclude that it is not possible at present to evaluate the clinical or epidemiologic significance of the surprisingly high incidence of reactions to histoplasmosis and blastomycosis as they occur singly or together in man in view of the demonstrated cross reaction between these antigens.

Since the publication of these two reports, the same lot of histoplasmin has been further tested by one of us (C. W. E.) on animals with other experimental mycoses and a cross reaction with *Candida albicans* was demonstrated. This fungus is known to be very commonly present in the sputum as a secondary invader in many kinds of pulmonary disease. Similarly it is not uncommon in thrush in infants and pregnant women and it is often present in the intestinal tract of normal individuals. If it is capable of sensitizing man to histoplasmin as it does guinea pigs, this may account for the high incidence of histoplasmin reactions observed. It is apparent that the histoplasmin used in these studies is not a specific diagnostic antigen.

In the two cases which occurred in siblings reported here (Cases 1 and 2) both were tested with histoplasmin in dilutions ranging from 1:1,000, 1:100, 1:10 and undiluted. However, in both cases the skin tests were negative in all dilutions. An interesting feature was that both parents of these siblings were positive in dilutions of 1:1,000. In the present state of our knowledge this is somewhat difficult to explain. It seems probable, however, that these patients were anergic since they were in the terminal stage of the infection when tested. An analogous situation would be the negative tuberculin reaction not uncommonly seen in overwhelming tuberculous infections.

Source of Infection.—The problem of the natural habitat of the fungus poses an interesting question. Histoplasmosis is known in man as a usually fatal disease, sporadic in appearance and world-wide in distribution. It frequently has been pointed out that perhaps histoplasmosis is not the highly fatal disease that the current mortality figures would indicate but that there may be a mild unrecognized form of the mycosis, that persons having the disease in this mild form transmit it to associates and that only the fatal cases are diagnosed and then only in the terminal stages or after death. While this possibility must be recognized, there is at present no convincing epidemiologic evidence that it is true. Two proved cases have not been recognized in one family except in Cases 1 and 2 reported here. We do not know of any other instance in which a patient with a proved diagnosis of histoplasmosis had any contact with another proved case. It is impossible at this time to determine whether the disease was transmitted from one of these brothers to the other. Obviously the opportunity for transmission was good because the boys slept together at a time when one of them had gastrointestinal symptoms. Transmission is theoretically possible, but if it commonly occurs it is not recognized. DeMonbreun⁵ found that the yeast-like form of *Histoplasma* remains viable after room drying for at least two months and will withstand 45° C. for thirty minutes although killed after ex-

posure to 55° C. for this period. The spores of the saprophytic growth phase are more resistant to both drying and heat.

The sporadic appearance of the mycosis without recognized association between cases of infection could be interpreted to indicate that it is not primarily a human disease and is not dependent upon an unbroken chain of human infections or human carriers. If this be true, the possible occurrence of some animal host or reservoir should be considered.

Histoplasmosis in the dog has been reported by several investigators and the dog is known as a susceptible laboratory animal, but it is not yet known whether this is a common disease of dogs, transmitted from dog to dog, or whether dog and man are infected rarely and perhaps by accident from a common source. The reports of a disease which was probably histoplasmosis in mice, rats, and a ferret, the susceptibility of mice to experimental histoplasmosis and the known susceptibility of some wild species of mice to a natural infection of coccidioidomycosis¹⁸ led to a search in the Ashburn area in Virginia for a rodent reservoir of histoplasmosis. A total of 114 rodents were trapped and examined by culture without finding the fungus. Pathologic studies on this series of rodents are not yet concluded.

The portal of entry of *Histoplasma capsulatum* is not known. Infected bites, ingestion, and inhalation have all been suggested as possible modes of entry with inhalation and ingestion the more likely possibilities. Parsons and Zarafonitis⁶ point out that the number of patients having lesions about the oropharynx, gastrointestinal ulcerations and lesions of the lungs would seem to indict the mouth and respiratory tract as the most likely possible foci of entry. Henderson and associates¹² believe that the very frequent involvement of the mesenteric lymph nodes is also to be considered strong presumptive evidence that the gastrointestinal tract is a portal of entry. These investigators have attempted to inject dogs and guinea pigs by the intratracheal route without success. Humphrey⁸ has drawn attention to the ear as a possible primary focus because of an associated otitis media or fungus infection of the ear noted before or during the course of illness in some of the reported cases. Because the disease has a predilection for the infant age group the possibility has been raised that domestic pets may account for the disease.

COURSE

The disease may have an acute onset and terminate rapidly while, on the other hand, it may appear in a chronic form with irregular exacerbations and long remissions. Humphrey⁸ has suggested that in certain instances the lesions may remain in an arrested state for some time or may undergo fibrosis with permanent cure as a result. In the review of seventy-one cases by Parsons and Zarafonitis⁶ the average course of the disease in thirty-nine cases with a duration of less than one year was five months, while four patients in this series were still living after two to six years. Of the age group under 12 years, the average duration of the disease was approximately three months.

Of the four cases reported here, one patient (Case 2) pursued a rapid fulminating course and died seven weeks after the onset of the illness. His

brother (Case 1) followed a considerably more chronic course, the disease process lasting one year. The duration of the disease in Cases 3 and 4 was seven months and eighteen months, respectively.

TREATMENT

Several types of therapy have been attempted in cases of histoplasmosis including sulfonamide drugs, quinine, ammonium, and potassium tartrate, arsenicals, pentnucleotide, iodides, and others. However, there have been no noticeable therapeutic effects from any of these drugs. In both Cases 1 and 2, sulfadiazine and penicillin were administered in large doses for a suitable interval without any overt influence on the course of the disease.

Neostam (stibium glucoside), an antimony compound, has been used in several cases with equivocal results. Mantell and associates¹⁹ report a case in which definite improvement was noted following its use. In a case treated by Palmer and associates²⁰ five injections of neostam were administered and the drug was then discontinued because it was poorly tolerated by the patient. However, at post-mortem examination *Histoplasma capsulatum* could not be found even though the organisms had been demonstrated in large numbers in a biopsy prior to the institution of therapy. The occasional encouraging outcome with neostam would indicate that it warrants further trial.

Roentgen therapy has also been used in histoplasmosis. Parsons reports a case in which irradiation was used in the treatment of enlarged lymph nodes which were thought to be due to lymphosarcoma; this produced a marked reduction in the size of the nodes. On post-mortem examination, this patient showed widespread histoplasmosis while no evidence of lymphosarcoma was found; presumably the lymph node enlargement had been due to histoplasmosis. The reduction in the size of the lymphadenopathy in this case is analogous to the effect noted in Case 1 of our series. This patient initially received 1200 r of roentgen therapy to the enlarged cervical nodes resulting in a prompt marked reduction in their size. However, the effect was only palliative and did not seem to alter the course of the disease. Unsuccessful use of x-ray in other cases has been reported.

SUMMARY

Four cases of histoplasmosis (two new and two previously reported) occurred in children living in a rural area in Loudoun County, Va., within a radius of ten miles of one another. The two new patients were brothers, constituting the first reported instance of histoplasmosis in siblings. *Histoplasma capsulatum* was isolated in culture premortem from both, although neither reacted to histoplasmin. The possibility of transmission from one brother to the other is considered. A search for an animal reservoir in this area was not successful. Histoplasmin reactions in guinea pigs with experimental moniliasis are reported. The skin reactions induced in other mycoses indicate that histoplasmin is not a suitable diagnostic agent.

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RHEUMATIC RECRUDESCENCES: DIAGNOSIS AND PREVENTION

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THE most characteristic feature of rheumatic infection, other than its propensity to involve cardiac structures, is its tendency to occur in repeated episodes. These recrudescences are responsible for both the high mortality and the morbidity of this disease, for less than 1 per cent of patients afflicted with acute rheumatic fever succumb during the initial attack, yet long-term follow-up studies disclose that from 25 to 40 per cent die within the ten to twenty years following the onset. It may be safely said that the tremendous spread between the immediate and the ultimate mortality is due to the profound tendency of this disease to strike in repeated episodes of rheumatic activity.

In order to emphasize again just how serious are these rheumatic infections of childhood, a fact appreciated by many but too often neglected by those concerned (including physicians), we must realize that few diseases, if any, surpass in magnitude this disorder as a cause of both death and disability in our children and young adults. Hence, in any given year it is not surprising to find that acute rheumatic fever and rheumatic heart disease account for more deaths in school-aged children than many of the much dreaded diseases of childhood. For example, the vital statistics of the United States (1943),¹ for children from 5 to 14 years of age, reveal that rheumatic fever and rheumatic heart disease caused more deaths (1,166) than all forms of tuberculosis (1,006). In fact the deaths from rheumatic infection were approximately the same as the total deaths (1,185) from poliomyelitis, diphtheria, measles, and scarlet fever. Martin² states that rheumatic infection is responsible for seven times as many deaths as is poliomyelitis.

To estimate the magnitude of rheumatic infection as a cause of disability, either acute or prolonged, is virtually impossible. This is in part due to the same reason which retards proper recognition from the medical profession as well as the general public. There is no limp or characteristic deformity to act as a cynosure. Were it true literally, rather than figuratively, that people "wear their hearts on their sleeves" it might be a different story. It is the examination of the heart by the physician which plays the most distinct role in evaluating the rheumatic fever problem, yet oftentimes a child escapes from the initial attack of rheumatic fever without evidence of heart involvement only to suffer a recrudescence with unequivocal signs of heart disease. Hence the estimation of disability, real and potential, is most difficult. Some idea of the significance of the problem may be deduced from data obtained during World War II.³ Cardiovascular disease was found to be the greatest single cause of total rejection in men from 19 to 26 years of age in the first draft. Subsequent study

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has revealed that rheumatic heart disease was responsible for the greatest portion of these rejections.

Similarly significant is the experience with the military services where the incidence of acute rheumatic fever has been surprisingly high in the various Army and Navy camps. Ordinarily this age group is not expected to have such a high proportion of individuals suffering an initial attack of acute rheumatic fever. The explanation offered is that actually these men were not undergoing an initial bout but were experiencing a recrudescence. This concept is borne out by the study of Master⁴ in a Naval hospital with eighty men, average age 21 years, who had acute rheumatic fever. He found that 54 per cent of the individuals gave the history of previous attacks. Inasmuch as 70 per cent of these attacks had occurred between the ages of 5 and 9 years, undoubtedly many of the other initial attacks had been forgotten. Here again the problem of rheumatic fever revolves on the focal feature of the disease, its proclivity to recrudescence.

In this presentation the matter of subsequent attacks of acute rheumatic fever—termed recurrences, recrudescences, exacerbations, or flare-ups—will be dealt with from the following considerations: General Features, Manifestations, Diagnosis, and Prevention.

GENERAL FEATURES

Number and Percentage of Recurrent Attacks.—There is a great variation in the actual number of recurrences which may range from one to six or ten or even more distinct episodes. The polycyclic nature of rheumatic infection often makes it difficult to determine whether or not an individual is suffering from a separate attack or simply a flare-up of a previous affliction. The vast majority of individuals, however, have more than one attack with the following percentages being noted by different authors:

AUTHOR	NUMBER OF CHILDREN	RECURRENCES
Roth and associates ⁵	488	68%
Bland and Jones ⁶	1,000	66%
Wilson ⁷	673	85%

Interval Between Attacks.—The most significant determinant of a recurrence is the time of the previous episode. This interval between attacks may vary from a few weeks to many years, but there is a greater likelihood of a recrudescence during the first year following any attack. It has been observed that two-thirds of the children having an attack will have recurrences within a 3-year period and four-fifths will have recurrences within five years. Roth and associates⁵ have stated that 73 per cent had recrudescences within three years after the initial attack. On the basis of Wilson's data the following ratios have been calculated:

Interval following attack	1	2	3 years
Likelihood of recurrence	3	: 2	: 1

Even though there is a greater likelihood of recrudescences within the few years immediately following an initial attack, the recent experience with the military

forces indicates that many years may elapse before a recurrence and that there is no reassurance of freedom from attacks during adolescence and young adulthood.

Relation to Age.—The peak age of rheumatic activity is from 11 to 13 years in contrast to the peak age of 6 to 8 years for the onset. Following the period of puberty, however, there appears to be a distinct decrease in the number of recrudescences. Hence, the earlier the onset the greater are the chances of recurrences; for example, a child having rheumatic fever at 5 years of age may have recurrences for six to eight years, while a 12-year-old child suffering his initial attack probably will have subsequent attacks only for two to four years. In a study of 337 rheumatic subjects, Wilson⁸ observed that the likelihood of a recurrence before and after 16 years of age was 5:1. Further calculations from her data show the following ratios for recurrences at progressive age groups:

Age in years	4-13	14-16	17-25
Ratio of recurrence	7	2	1

MANIFESTATIONS

The manifestations of rheumatic fever recurrences are just as protean as those of the initial episodes. For descriptive purposes, because of the extreme variability in manifestations, recurrences may be classified as major, minor, or possible recrudescences. When the manifestations are more severe, including carditis, polyarthritis, subcutaneous nodules, or severe chorea, the attack may be considered a major recrudescence. If there are but mild joint pains, a mild chorea, or mild constitutional symptoms, with little evidence of carditis, only a minor recrudescence has occurred. At times, however, this symptomatology is only suggestive of a rheumatic flare-up, hence is referred to as a possible recrudescence. It should be emphasized that the chances of a recurrence are fully as great after a minor attack as after a major manifestation.

It has often been stated that a recrudescence is likely to manifest itself similarly to the initial attack; however, a critical study of recurrent episodes discloses a rather widespread incidence for all types of manifestations, particularly as the disease progresses through recurrences. This fact is well illustrated in Table I where the incidence of types of manifestations for the first attack is contrasted with that found to occur during the entire rheumatic career.

The types of manifestations at onset offer no criteria for the development of recrudescences. Subsequent attacks are equally likely to occur after poly-

TABLE I. INCIDENCE OF TYPES OF MANIFESTATIONS OF RHEUMATIC FEVER CHARACTERIZING THE FIRST ATTACK AND OCCURRING THROUGHOUT THE ENTIRE CAREER OF THE DISEASE

INCIDENCE (IN PER CENT)	PAIN			EN- CEPH- ALITIS	NOD- ULES	CARDITIS				SKIN
	EXTREMITIES		ABDO- MEN			MARKED	MURMUR (ALONE)	WITH POLY- ARTHRITIS AND/OR CHOREA	CONGES- TIVE FAIL- URE	
	MILD	POLY- ARTHRITIS								
				CHO- REA	SUB- CU- TA- NEOUS					
First attack	25	25	?	25	3	3	10	15	<1	3
Throughout entire course	67	66	13	40-48	12-19	72-83	10-20	?	26	12

arthritis, chorea, or carditis. Thus, no predictions for future progress can be set up on the basis of any individual type or group of manifestations.

DIAGNOSIS

The lack of any specific laboratory tests, together with the varied symptomatology and manifestations of rheumatic infection, places the diagnosis on a strictly clinical basis. Other than the presence of the subcutaneous fibroid nodules, which are almost pathognomonic of the disease, there are no features which are such that the diagnosis can be made unequivocally. Just as in arriving at any other diagnosis in clinical medicine, it is necessary to gather all information possible from the history, physical examination, and laboratory procedures, with a critical evaluation of these data, in order to come to the correct conclusion. Many of my medical colleagues frequently decry the lack of some specific test for rheumatic fever; this remark is usually countered with the statement that it is perhaps fortunate there are still some conditions which require critical clinical interpretation. Nonetheless, if such a specific test were developed, the conquering of this devastating condition would be greatly facilitated. Certainly one feature is true, namely, the physician is the only one with the necessary experience and knowledge to make this diagnosis.

A complete consideration of the significant features of anamnesis and clinical study are not indicated in this review; however, the author has found it very useful in dealing with medical students to list pertinent features of the history, examination, and laboratory, and to mark these as positive or negative under the heading of rheumatic and nonrheumatic.

Suffice it to say that in making the diagnosis of a rheumatic recrudescence the knowledge of a previous rheumatic episode is very beneficial. Likewise a positive family history for rheumatic fever is often helpful. The history of the occurrence of the initiating upper respiratory tract infection with hemolytic streptococci is not as frequently obtained as that reported by the exhaustive studies of the military personnel. Jones,⁹ however, was able to find evidence of the precipitating respiratory tract infection in two-thirds of his series of 271 recrudescences.

Inasmuch as the criteria for diagnosis of a recrudescence are fundamentally the same as for the initial episode, some consideration may be given to the problem of differential diagnosis as observed during a fourteen-year period in the heart clinic of the department of pediatrics at the University of Minnesota. This will be discussed from the following viewpoints: (1) various disorders, mentioned in standard references, which may simulate rheumatic infection; (2) specific diagnoses which have been made when rheumatic fever actually was the cause of the clinical picture; (3) diagnosis of rheumatic fever made when in reality some other disorder was responsible for the condition; and (4) summary of the conditions especially offering confusion in the differential diagnosis of rheumatic fever.

Disorders Simulating Rheumatic Infection.—In 1941 a study¹⁰ was made of the conditions which have been mentioned in various textbooks and articles as being of possible significance in the differential diagnosis of rheumatic fever.

TABLE II. COMPILATION FROM STANDARD REFERENCES OF DISORDERS WHICH POSSIBLY MAY BE OF SIGNIFICANCE IN RELATION TO THE DIFFERENTIAL DIAGNOSIS OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

<i>Pain</i>	<i>Cardiac Symptoms</i>
Trauma (sprain)	Congenital heart disease
Myositis	Diphtheritic myocarditis
Purpura—anaphylactoid	Interstitial myocarditis
Leucemia	Tuberculous pericarditis
Appendicitis	Suppurative pericarditis
Osteomyelitis	Subacute bacterial endocarditis
Poliomyelitis	Gonococcic carditis
Osteochondritis	Glycogen storage disease
Rheumatoid arthritis	Accidental or functional murmur
Tuberculous arthritis	Psychic tachycardia
Syphilitic arthritis	Beriberi
Gonococcic arthritis	Anemia
Septic arthritis	Pleurisy
Scurvy	Pneumonia
Malaria	Rhabdomyoma
Pyuria	Scoliosis and chest deformity
Bacteriemia	Idiopathic hypertrophy
Upper respiratory tract infections	
Hemorrhagic diseases	<i>Chorea</i>
Erythromelalgia	Multiple neuritis
Trichinosis	Habit spasm
Glandular fever	Imitation
Brucellosis	Encephalitis
Serum sickness	Athetoid movements
Growing pains	Dystonia musculorum deformans
	Poliomyelitis
<i>Miscellaneous</i>	Familial ataxia
Typhoid and paratyphoid fever	Nervousness
Erythema nodosum and multiforme	Vascular cerebral lesions
Meningococcemia	Hyperthyroidism
Sickle-cell anemia	Myxedema of adolescence
Acute glomerular nephritis	Hysteria
Hodgkin's disease	Poisoning
Periarteritis nodosa	Brain tumor
	Friedreich's ataxia
<i>Subcutaneous Fibroid Nodules</i>	
Rheumatoid arthritis (rare)	

For the sake of completeness these are listed in Table II under the more or less general categories of the following dominant types of rheumatic manifestations: pain, cardiac symptoms, chorea, and miscellaneous. It is all too obvious that there is a potentiality of from fifty to sixty disorders which possibly could be confused with some phase of rheumatic infection.

Specific Diagnoses Made Instead of Rheumatic Fever.—The referring or admitting diagnoses have been analyzed for about 300 children with rheumatic fever. After the cases had been carefully studied, the conclusion reached was the same as the initial diagnosis in two-thirds of the cases. Although in a few instances the correct diagnosis could have been made if a little more thought had been given to the problem, there were still one-fourth to one-third of the children studied in whom making the exact diagnosis was a real problem. Since these data have been previously reported¹¹ a detailed consideration need not be repeated; however, a brief summary is significant. In Table III the confused diagnoses have been grouped according to the general types of rheumatic manifestations, and the relative percentages of occurrence are listed for each group.

TABLE III. DISTRIBUTION OF THE DISEASES WHICH HAVE BEEN GIVEN AS THE DIAGNOSIS INSTEAD OF THE CORRECT DIAGNOSIS OF RHEUMATIC FEVER

RHEUMATIC MANIFESTATION	CONFUSED DIAGNOSIS	PER CENT OF TOTAL INCORRECT DIAGNOSES
Pain	Poliomyelitis 5	34
	Osteomyelitis 4	
	Appendicitis 25	
Encephalitis	Nervous	23
	Emotional	
	Neuritis	
	Speech disorder	
Carditis	Septicemia	22
	Bacterial endocarditis	
	Pneumonia	
	Pleurisy with effusion	
	Congenital heart disease	
Skin	Erythema	4
	Purpura	
Kidney	Nephritis	5
General	Low-grade infections	11

Diagnosis of Rheumatic Fever Made Incorrectly.—Consecutive hospital records have been studied¹² for 982 children about one-half of whom were of the school ages from 5 to 15 years. Of these, rheumatic fever was the admitting diagnosis in 3 per cent of the cases. If such obvious diagnoses as congenital defects, fractures, and diabetes are excluded, rheumatic fever was the admitting diagnosis in 10 per cent of all school-aged children. The corrected diagnoses had the following frequency in occurrence:

Acute osteomyelitis	4 cases
Hyperthyroidism	3 cases
Leucemia	2 cases
Acute glomerular nephritis	2 cases
Poliomyelitis	1 case
Hodgkin's disease	1 case
Hysteria	1 case
Catarrhal jaundice	1 case
Chronic infectious arthritis	1 case
Recurrent tonsillitis	1 case
Idiopathic hypoprothrombinemia	1 case
Parulent pericarditis	1 case
Toxic myocarditis, post-scarlet	1 case

Conditions Important in Differential Diagnosis.—In summary those disorders which are especially to be considered in arriving at a diagnosis of rheumatic fever are presented in Table IV. On the basis of all the data available, together with clinical experience, the more significant disorders are grouped in accordance with the dominant types of rheumatic manifestations. It should be pointed out, however, that these are not strict groupings, as, for example, patients with sickle-cell anemia, leucemia, nephritis, and Hodgkin's disease may have pain as a prominent symptom. Likewise, even in rheumatic encephalitis, abdominal pain has been a dominant feature, in fact, acute appendicitis was the diagnosis of four of nineteen chorea patients for whom incorrect diagnoses had been made. Obviously geographic conditions vary the relative importance of these disorders to be considered in the differential diagnosis. At the Children's Hospital, University of Texas, sickle-cell anemia

TABLE IV. SUMMARY OF THE DISTURBANCES MOST LIKELY TO CAUSE CONFUSION IN THE DIFFERENTIAL DIAGNOSIS OF RHEUMATIC FEVER

<i>Pain</i>	<i>Encephalitis</i>
Appendicitis	Hyperthyroidism
Poliomyelitis	Emotional problems
Osteomyelitis	<i>Skin</i>
Rheumatoid arthritis	Erythema
Meningococcemia	Purpura
<i>Carditis</i>	<i>General</i>
Sickle-cell anemia	Low-grade infections
Bacterial endocarditis	Fulminating infections
Congenital heart disease	Sepsis
Leucemia	Pneumonia
<i>Kidney</i>	Hodgkin's disease
Nephritis	

at times is almost impossible to differentiate from rheumatic infection. Seasonal variations also influence these diagnoses. It has been observed that during the late summer months poliomyelitis is more frequently incorrectly diagnosed for patients who actually have rheumatic fever. This has been true particularly since Sister Kenny has advocated the importance of early treatment of this disease.

PREVENTION

The severity of prognosis for rheumatic infections is proportionate to the number of recrudescences in regard to both the mortality and the degree of cardiac disability. With each flare-up of the condition the likelihood of carditis becomes greater. Wilson⁷ observed in 246 patients with carditis that the mortality was 20 per cent when there was but one attack, in contrast to 64 per cent after four or more attacks. Thus, anything which can be done to prevent recrudescences is mandatory.

It is particularly heartening to note that during the past decade distinct advances have been made in this direction. Our purpose at present is to review measures which have been directed toward the problem of lessening the frequency of occurrence of rheumatic episodes. These will be discussed under the following topics: (1) convalescent care; (2) climate; (3) foci of infection; (4) avoidance of upper respiratory infections; and (5) methods based on the present concept of pathogenesis.

Convalescent Care.—It has been amply demonstrated that proper convalescent care is valuable for patients with rheumatic infections. The gradual resumption of physical activity must be properly controlled with adequate rest, a nutritious diet, and satisfactory hygienic conditions to promote health and vitality. Provision must be made for education and for occupational and play therapy which will help in the psychologic adjustment of the child. All measures should be aimed toward preventing the development of the undesirable state of chronic invalidism. No critical study has been made of the various types of prolonged convalescent care regarding their effect upon the development of recrudescences. Taran,¹³ in a three-year study of 110 rheumatic children from 6 to 14 years of age, given the benefit of care in a cardiac sanatorium, found the recurrences in this group were but one-half as frequent as those in a group of clinic patients living at home. Although it is well

recognized that special convalescent homes thus can offer certain advantages for the rheumatic patient, the availability of such institutions is still far short of the need for them, and the brunt of the problem of preventing recrudescences must be borne by the physician directing the care of his patients in their private homes.

Climate.—For the favored few who are economically able to move to geographic areas where rheumatic fever is less prevalent, something may be gained in the prevention of recurrences. The effect of climate upon rheumatic fever can be illustrated by the death rates from heart disease in school-aged children for different parts of the United States. These mortality rates for 1940¹ were as follows: Middle Atlantic States, 11.3; Mountain States, 10.8; New England States, 7.4; West North Central States, 6.9; West South Central States, 5.4; and Pacific States, 4.6.

Unfortunately, controlled long-period studies have not been made to compare the mortality and morbidity between individuals who have been transplanted to new localities and those who have remained in the original environment. This would be particularly important in view of some of the newer developments in the field of rheumatic prophylaxis. The author has been impressed with the prevalence of rheumatic fever in the gulf coast region of Texas. In a relatively small service at the Children's Hospital in Galveston, on several occasions as many as one-half of the children of school age on the wards were suffering from acute rheumatic infections. Similar personal observations have been made by Platou in New Orleans and Fashena in Dallas. Suffice it to say that even if the ideal geographic area for prevention of rheumatic recrudescences could be found, economic and social factors would preclude this as the solution to the rheumatic fever problem for the general public.

Foci of Infection.—Removal of such foci as infected teeth, tonsils, or sinuses has been advocated as a means of preventing recrudescences. Data concerning the significance of the sinuses and teeth in this regard are not available. Abundant evidence, however, has been brought forth to indicate that tonsillectomies and adenoidectomies, per se, are without influence upon the frequency of rheumatic episodes. The indications for removal of the faucial tissue are independent of the rheumatic infection. If tonsils are to be removed, a number of workers advocate the use of prophylactic sulfonamide therapy as a safeguard against a flare-up of the rheumatic infection. Likewise, in extraction of infected teeth, it is wise to give the benefit afforded by protective prophylactic measures.

Avoidance of Upper Respiratory Infections.—This is one of the most glib bits of advice given by physicians, but rarely are the means described by which it can be accomplished. True enough, if it were possible to prevent the occurrence of upper respiratory infections, undoubtedly the majority of rheumatic recrudescences would not develop. The general rules of avoiding contacts with such infections, preventing chilling and exposure, employing recognized standards for hygienic care and nutrition, and obtaining adequate rest can be advised without the patient being able from a practical viewpoint to accomplish the desired result. There is the hope for the future that specific achieve-

ments in this direction may be realized. Inasmuch as hemolytic streptococci appear to play an important role in the pathogenesis of this disease, much might be accomplished if upper respiratory infections actually could be avoided.

Methods Based on the Present Concept of Pathogenesis.—The exact role played by hemolytic streptococci in the etiology of rheumatic infection is not entirely clear, but it is quite generally accepted that this type of organism is implicated in the pathogenesis of the disease. Certainly the methods of prevention of recrudescences which have shown the most promise are based on the streptococcic theory. The modern concept of the chain of events which results in the production of the rheumatic state may be summarized briefly as follows: First, there is an initiating upper respiratory tract infection, caused by certain types of hemolytic streptococci, the duration of which is from one to three days. Second, a latent interval follows of from one to three weeks, during which time some phenomenon, immunologic, allergic, or otherwise, takes place. Third, the clinical manifestations of the rheumatic infection become apparent with varying degrees of severity. Carefully controlled studies¹⁴ by the military authorities in World War II indicated that 90 per cent of the youths who suffered attacks of rheumatic fever while in certain army camps had experienced such previous streptococcic infections, with an average latent interval of sixteen days until the symptoms of rheumatic fever developed. Not all individuals, however, who have had a streptococcic infection will develop rheumatic fever; in fact, it has been estimated that only about 5 per cent of those with such infections, proved by throat cultures and increases in the blood antistreptolysin titer, will undergo a rheumatic progression. This selectivity for certain individuals manifesting the subsequent rheumatic infection possibly may be explained on the constitutional basis which allows a characteristic tissue response or reaction to certain organisms or their products. The familial incidence of this disease supports this view of a hereditary factor responsible for the peculiar chain of events characterizing rheumatic fever. Wilson's⁷ studies especially are convincing. Strictly speaking, even the climatic and geographic factors in regard to recrudescences can be explained on the basis of streptococcic pathogenesis, and the same may be said regarding "avoidance of upper respiratory infections," which really means to avoid streptococcic throat infections.

Three methods of preventing rheumatic recrudescences, based on these concepts, have been used during the past few years. (1) The salicylate method is assumed to act by preventing the antigen-antibody reaction which produces the pathologic changes in the tissues. (2) The administration of streptococcic toxins is aimed at building up protection in the body to the streptococcus organism. (3) The continuous administration of sulfonamide compounds is believed to have a favorable effect due to suppressing the growth of the streptococci before they are able to develop sufficiently to initiate the chain of events which results in active rheumatic fever. It has been observed that sulfonamide administration will not prevent the recrudescence if started after the onset of the initiating streptococcic throat infection. The process has been compared to a bomb exploded by a fuse, the sulfonamides being completely ineffective

once the fuse has been lighted. (4) It is conceivable that penicillin similarly might be advantageous for prophylaxis of rheumatic recrudesences, but we have seen no reports in this regard.

Salicylate Administration.—Based on the hypothesis that salicylate administration prevents serum sickness from developing, possibly by interfering with the antigen-antibody precipitation, and that the tissue response in rheumatic infection results from such an antigen-antibody reaction. Coburn and Moore¹⁵ carried on a laboratory and clinical study with a group of patients considered as likely to develop rheumatic recrudesences. They found that daily salicylate doses prevented the formation of precipitins but did not hinder the development of antistreptolysins. Concerning the clinical aspect of the problem, these workers administered from 4 to 6 Gm. (2 to 4 Gm. for children) of sodium salicylate daily for a month to 47 rheumatic subjects quiescent as regards activity of the infection, but who had acquired a Group A hemolytic streptococcal pharyngitis proved by throat cultures as well as clinical observations. It was found that 46 of these 47 individuals escaped the development of a rheumatic flare-up. In contrast, rheumatic recrudesences did develop in 57 out of 139 control subjects, not receiving salicylates following their attacks of streptococcal pharyngitis. A few other workers, however, who have attempted to use salicylates as a means of preventing rheumatic flare-ups, have not had the success reported by Coburn and Moore. Pennoyer and Hansen¹⁶ attempted to carry on such a routine in an outpatient rheumatic fever clinic but were partially unsuccessful because of the lack of cooperation in having the children brought into the dispensary or hospital at the time they suffered upper respiratory tract infections. It is difficult for the average physician to obtain the necessary throat cultures and the typing of these for Group A hemolytic streptococci in order to use effectively this type of prophylaxis. It is hoped that further work on the problem will enhance this method of prevention, but we must recall that administration of large doses of salicylates for prolonged periods is not without danger in some instances.

Biologic Methods of Prevention.—For many years workers have attempted to develop protective antibodies in patients with rheumatic fever by the administration of streptococcal toxins. The most encouraging work reported in this direction is that of Wasson and Brown.¹⁷ These authors administered a tannic acid precipitated toxin of certain strains of hemolytic streptococci at three-week intervals in 5,000, 8,000, 10,000, and 12,000 skin test doses, with the final dosage repeated at six-month intervals. In the 73 season cases so treated during 1940-1942, only 2 rheumatic recrudesences were observed, whereas in the control series comprising 60 season cases, 17 recrudesences developed with 3 deaths. It is hoped that further work with the immunologic type of prevention will justify more wide use of this method.

Prevention With Continuous Sulfonamide Administration.—In the early days of sulfonamide therapy, Dr. Paul Dwan and the author instituted sulfonamide administration to a small group of patients but interrupted the study because of the increasing reports of possible deleterious effect of the then new type of drug. After learning of the apparent success of Coburn and Moore¹⁸ as

well as Thomas and France¹⁹ another study was instituted and reported by Hansen, Platou, and Dwan²⁰ with a follow-up report by Pennoyer and Hansen.¹⁶ This study was conducted in an outpatient dispensary. Although various workers have carried out better controlled studies with more complete laboratory data, it was felt that the results from conditions closely analogous to office practice with children might have special significance for the average physician. Our findings have been in essential agreement with those of other investigators. There were 27 recrudescences observed in 58 patient-seasons in the control group and 7 recurrences in 131 patient-seasons for those who received a sulfonamide compound prophylactically. Included in the series were some patients who, we had reason to believe, were not taking the drug regularly. In fact, in most instances of recurrences for the treated group the drug was taken irregularly, inadequately, or temporarily discontinued by the patients. Pennoyer and Hansen observed that the factors responsible for this situation were: (1) Failure to understand that the drug was to be taken continuously. (2) Indifference on the part of the patient or his parents. (3) Transportation difficulties, contingent upon gas rationing, interfering with appointments and refilling of prescriptions. (4) Discontinuance of the medication by family physicians who were not familiar with the rationale of the procedure. More surprising than these failures, however, was the excellent cooperation displayed by most of the patients under observation.

We have summarized briefly in Table V the results reported by various workers who have studied sulfonamide prophylaxis. The over-all experience comprises a total of 1,561 patient-seasons. These are mostly with children,

TABLE V. THE INCIDENCE OF RHEUMATIC RECRUDESCENCES AS INFLUENCED BY CONTINUOUS ADMINISTRATION OF SULFONAMIDE COMPOUNDS

AUTHOR	SULFONAMIDE TREATED		CONTROL	
	PATIENT SEASONS	RECURRENCES	PATIENT SEASONS	RECURRENCES
Thomas, and associates ²¹	114	2	150	21
Coburn and Moore ¹⁸	189	1	146	31
Stowell and Button, Jr. ²²	7	1	14	4
Kuttner and Reyersbach ²³	108	1	104	28
Chandler and Taussig ²⁴	41	1	41	5
Feldt ²⁵	89	0	42	3
Dodge, and associates ²⁶	181	4	136	19
Messeloff and Robbins ²⁷	25	1	30	2
Hansen and associates ²⁰	78	2	46	21
Total	852	13	709	134

but some of the studies have included older individuals who were quiescent rheumatic subjects. The incidence of recurrences of 1.5 per cent for the sulfonamide treated group stands in distinct contrast to 19 per cent for the control group, and seems to offer quite convincing proof that a practical means has been found to prevent rheumatic recrudescences. It is admitted that continuous medication of this type is not the ideal perhaps, but it is surprising how relatively few toxic reactions have been reported.

In order to evaluate fully whether or not this is the answer to prevention of rheumatic recrudescences, long-term studies will have to be carried on to

determine: (1) Is the mortality actually reduced, and (2) is the degree of cardiac disability actually lessened? Most workers are quite convinced of the value. Pennoyer and Hansen surveyed the number of deaths from rheumatic fever and rheumatic heart disease which occurred on the pediatric service at the University of Minnesota. In 1938, 1939, and 1940 there were 5, 9, and 13 deaths, respectively, attributed to this cause. By this time a fairly large portion of the rheumatic children were being given sulfonamides. In 1941, 1942, and 1943 the deaths from rheumatic fever were 1, 3, and 2, respectively, and in these none of the children had been given the advantage of sulfonamide prophylaxis. It may be of interest to note that the mortality rates for rheumatic fever deaths in children have been decreasing during the past few years. There were 1,662 such deaths in the United States in 1940, 1,399 deaths in 1941, and 1,166 deaths in 1943. It is possible only to conjecture that this trend might be attributable in part to the increased use of prophylactic measures in reference to rheumatic recrudescences. The author has become convinced further of the necessity for prophylactic measures from experience gained at the Children's Hospital at the University of Texas School of Medicine in Galveston. A surprising number of children suffering from rheumatic recrudescences have been on the service here, and the number of deaths in such recurrences has been greater than had been expected in an institution so favorably located in the Southland.

The general recommendations which seem advisable in regard to employing sulfonamides for the prevention of rheumatic recrudescences may be summarized as follows:

1. The patient should be free from evidence of rheumatic activity.
 2. The parent as well as the patient should have a clear idea of the purpose and reasons for the undertaking and in turn the physician should have assurance from them that proper cooperation will be forthcoming.
 3. Periodic examinations, at first, every week for three to four weeks, then at four- or possibly six-week intervals. In addition to the careful physical examination, the hemoglobin, leucocyte, and differential white cell counts and urinalysis should be followed in order to detect signs of toxicity or idiosyncrasy to the drug. If it is possible to determine the sulfonamide level in the blood, it is recommended that this be done. Levels should be maintained between 1 and 3 mg. per 100 c.c. of blood. This serves as a means of determining the degree of cooperation the patient is exercising, although the urinary excretion of the drug may also be used for this purpose.
 4. Choice of drug and dosage.
 - a. Sulfanilamide—0.6 Gm. with the morning and evening meals for those over 9 to 10 years, or 0.3 Gm. with each meal for those under this age.
 - b. Sulfadiazine or sulfamerazine—1.0 Gm. daily, in one or two doses, for those over 9 to 10 years, or 0.5 Gm. daily for those under this age.
- It probably will be some years before it is determined how long sulfonamide prophylaxis should be continued. There appears to be no special danger from administering the drug continuously in these amounts. Some children have

maintained themselves for periods of five to six years, some possibly longer, with apparently no harmful effects. Since the incidence of rheumatic recrudescences is considerably less after 16 years of age and 80 per cent of the recrudescences develop within five years after a rheumatic attack, it would seem that prophylactic measures should be carried out for at least five years after the rheumatic attack or until reaching 17 years of age. The studies of Coburn and Moore,¹⁸ also Thomas and associates,²¹ appear to indicate, however, that the same regime could be effective during adolescence and in young adulthood. It is hoped that future studies will clarify this point, at least until some superior method of prevention is developed.

We may close our discussion with the statement that a means of prevention of rheumatic recrudescences in children appears to have been found which can be carried on in an office practice, but this should be done only under the direction of the physician, and he should assume full responsibility by keeping the patient under his critical scrutiny at all times. In fact, the rheumatic subject should be as carefully treated as the diabetic, and should be maintained under continuous medical supervision. If these suggestions were fulfilled much could be accomplished in the way of prevention of rheumatic recrudescences.

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THE PEDIATRICIAN'S RESPONSIBILITIES IN THE DIAGNOSIS AND TREATMENT OF EARLY POLIOMYELITIS

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THE pediatrician's responsibilities in the diagnosis and early care of poliomyelitis are extensive, varied, and manifold. In this paper an attempt will be made to discuss some of the more important.

Many of the diagnoses are easily made by any doctor. Although no symptom, sign, or test proves the diagnosis, there is usually enough circumstantial evidence in headache, fever, vomiting, stiffness in neck, back, hamstrings, and other muscles, and also apparent muscular disability, to lead a physician at least to suspect the disease. The diagnosis is strengthened, in fact pretty much confirmed, by the finding in the spinal fluid of a slight or moderate increase in cells. Since the proportion of cases is increasing in young adults who are first seen by internists or general practitioners, the pediatrician is not always called upon to make the diagnosis. But these adult patients are apt to be admitted along with children to poliomyelitis services where a pediatrician is usually in charge and thus has the opportunity and responsibility to confirm the diagnosis and initiate treatment.

For each such new case, the responsibility at once arises for checking over the rest of the patient's family to seek out other possible illnesses that might be overlooked instances of infantile paralysis. Where there are small children it will be usual to find such cases, most commonly in the nonparalytic form. Multiple family cases are more and more being recognized, and it is now a well-known fact that the case of poliomyelitis with recognizable loss of strength is the infrequent case—the so-called “medical accident.”

When poliomyelitis has been identified and the patient usually hospitalized, the pediatrician becomes the coordinator and often the initiator of all types of care: pediatric, nursing, physical therapy, occupational therapy, morale building and social rehabilitation, and finally orthopedic support and reconstruction. There are few if any illnesses in the treatment of which so much must be done by so many different specialists. It is obvious that one person must be responsible for the proper coordination of all these efforts being made in the patient's behalf.

In the average spinal case with involvement of a leg or an arm, the coordination of care becomes a matter of routine. A schedule of rest and relaxation, of proper nursing care, and of measures to combat increased muscle tension can be quickly and adequately instituted by any doctor at all familiar with the infection. But there are special manifestations of the disease the management of which requires experience, judgment, and skill. In general these are associated with bulbar cases and those with respiratory difficulties. Here the proper

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coordination of efforts may be lifesaving, or at least may help to minimize the aftereffects of the disease—to lessen the irreparable destruction found after the tidal wave of the acute infection has passed away.

Bulbar involvement is not usually difficult to determine. In addition to considerable fever, prostration, and a look of toxicity, there may be nasal regurgitation of fluid, a change in the quality of the voice, a lag in the motion of the palate with loss of the gag reflex; also accumulation in the pharynx of mucus, often sticky, increasing difficulty in swallowing, an increased rate and thready quality of the pulse; at times a temporary increase in the blood pressure, and then too often the development of a dusky pallor as the respiratory and cardiac centers fail to produce enough oxygenation.

The care of bulbar cases, especially those with extensive manifestations, involves many measures; among others being first reassurance of the patient, then the prevention of aspiration of food or mucus into the lungs, the provision of adequate oxygenation, the support of the heart, and if possible, the reduction of intracranial edema. It is of special importance that these patients be handled no more than is absolutely necessary. In case of uncertainty as to what to do, it is better to do nothing than to do something not needed: that is, "In case of doubt, don't." Or as the fracture surgeons say: "If you can't help, don't hinder." However, the bladder and bowel must not be allowed to remain distended, and attempts must be made to meet, at least to some extent, the patient's requirements for fluid, calories, and nitrogen balance.

In the care of these bulbar cases, an important part of the treatment is concerned with attempts at combating with dehydration the edema of the central nervous system. While the immediate result of the intravenous injection of markedly hypertonic solutions such as 50 per cent glucose, or those containing electrolytes, may appear beneficial in lowering blood pressure, lessening headache, and in general improvement of the patient, we have been told that there may be a "rebound" a few hours later to a worse state than before. We have been using intravenous injections of 10 per cent glucose, but there may be better measures, such as giving by mouth or gavage repeated small amounts, for instance 1 ounce, of a saturated solution of magnesium sulfate which is not absorbed from the alimentary canal and which promotes fluid elimination by the bowel.

In poliomyelitis patients with any form of respiratory difficulty, the responsibility of the pediatrician is great. He must first determine for each patient which factors are responsible for the inefficient breathing and what are their relative importance. These may be: first, damage of the respiratory center in the medulla—a very grave condition; second, pharyngeal involvement with accumulation of mucus in the airways mechanically obstructing breathing; third, any muscular tightness which may interfere with expansion or contraction of the thoracic cage; fourth, impairment of innervation of the muscles of breathing; and, fifth, a factor often not considered adequately, emotional disturbances—fear, panic, hysteria. Two or more of these five factors are usually present together, but for purposes of treatment it is of the utmost impor-

tance to recognize which factors should have primary consideration. For example, a bulbar patient who can neither cough nor swallow and who has much mucus in his pharynx will practically invariably do badly in a respirator, which, on the other hand, may save the life of a spinal patient who has so extensive a loss of innervation of the muscles of breathing that he will die of suffocation unless he is given prolonged artificial respiration.

The emotional disturbances that are always present in patients struggling for air often receive inadequate consideration. Time and again a panicky child, or even adult, who seems unable to get enough oxygen, can be calmed and steadied and enabled to breathe more efficiently by the inspiring and soothing influence of an expert doctor or nurse. Similarly, a patient who is obviously going to need a respirator will more rapidly relax and let the machine do the work if he is told in advance what to expect, and that he is merely to be given a little rest for a while, thereby allaying his fears.

Such decisions as when to put a patient in a respirator, and when not, when to take him out, when and how to give him oxygen, when and what fluids to give him, and what stimulation to use are all responsibilities the pediatrician must shoulder. Nor can one be dogmatic in stating what should be done. We believe there are good reasons for being very slow about putting a patient in a respirator so we usually wait until it is obvious that he cannot go longer without it, and we try to take him out later in the same day. We know there are those who advocate putting immediately into a respirator a patient with even a minimum of respiratory difficulty. We very freely give wet oxygen by nasal catheter, and we believe caffeine is our best cardiac center stimulant, especially when supplemented by oxygen therapy. When we do use a respirator, we run it at the lowest negative pressure that will keep the patient oxygenated and at the rate he finds most comfortable. We believe positive pressure is contraindicated. Incidentally, any person who is going to supervise the care of a patient in a respirator should first himself experience having artificial respiration given him by such a machine.

There are a number of factors in the care of patients both while in a respirator and particularly after such a stay, that require special knowledge and consideration. Most of these patients cannot cough because of diaphragmatic weakness and there is the constant danger of a mucous plug in a bronchus, causing the sudden development of a massive atelectasis. A respiratory infection is, therefore, a serious complication in these patients. Many post-respirator patients develop hypertension, possibly due to chronic anoxia and passive congestion of the brain. Some have myocardial damage, determinable only by the electrocardiogram.

The function of the diaphragm must be carefully studied, as with a fluoroscope. Sometimes one half is found to be immobile, presumably in spasm; the other half flapping up and down, and therefore of no help to such intercostal breathing as may be present. We are finding the use of blow-bottles very helpful in aiding postrespirator patients to increase the use of their diaphragms and thus to increase their vital capacities.

Aside from the management of poliomyelitis itself, a ward full of such patients offers a pediatrician many interesting problems. In one small series of thirty or so cases this fall, we have had patients allergic to wool and to food, problems of over- and undernutrition, and a diabetic patient whose insulin dosage was disturbed by physiotherapy. We have had behavior problems, upper respiratory infections, kidney conditions—notably hematurias—and a number of skin abnormalities and single instances of various other problems.

The pediatrician must also constantly guard against cross-infections among the patients, and especially strive to prevent the spread of poliomyelitis itself to those not yet afflicted. Rigid individual isolation at least for the first week is observed, because washings of the nasopharynx of patients have been shown to contain the virus during that period, but precautions against fecal contamination should be observed for a much longer time; some authorities say for at least two months.

When poliomyelitis has struck, three great responsibilities in the matter of education belong to the pediatrician. Inasmuch as there is pretty general agreement that the sooner a poliomyelitis patient is put to rest the better is his prognosis, it is highly important particularly in the presence of the disease that parents be educated to put to bed at once any person who has acute illness, no matter how trivial. An apparent attack of indigestion, a head cold, or more especially a fever and headache may be an oncoming poliomyelitis. Many illustrations may be quoted of such patients who tried to continue normal activities and then developed serious, even fatal cases of this malady.

In the second place, parents need to be taught the nature of the disease and the aims of physiotherapy so that they can better cooperate in the treatment of muscle tightness and the re-education of muscle functions.

Perhaps the most important aspect of education, however, is in the field of morale. Parents need to be taught that patients left with weakened muscles must learn to be as self-sufficient as possible; must be encouraged to overcome their restrictions and to press on to achieve lives of usefulness to others and satisfaction to themselves. The pediatrician can find in this realm of morale-building his finest and most rewarding opportunities of service.

Thus, a group of poliomyelitis patients offer a pediatrician unusually varied and challenging responsibilities. In cases with bulbar and respiratory difficulties his skill may save life. For the many exigencies and complications that may arise, his constant supervision is essential. For tying together the work of the many specialists who help in the treatment, his coordination of their efforts, and consideration of the patient as a whole are vital. For protecting and informing the community his duty is clear. Thus, although one's sympathies are constantly being aroused and one's emotions stirred, a pediatrician can well find satisfaction in serving the poliomyelitis patient.

THE RELATIONSHIP OF INFANTILE PARALYSIS EPIDEMICS TO COMMUNITY RESOURCES IN THE TREATMENT OF PATIENTS

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SINCE the severe epidemic of 1916 certain areas in the United States have had a relatively low incidence of infantile paralysis, despite frequently recurring major epidemics in adjacent areas. The city of Rochester, N. Y., and the surrounding countryside for a radius of approximately one hundred miles was one of those regions which remained relatively immune to attacks during the annual recurrence of this disease for a period of nearly thirty years.

For a period of twenty-eight years following the 1916 epidemic there was an average of 11 cases reported in Rochester, N. Y., 31 cases in Syracuse, N. Y., 38 cases in Buffalo, N. Y., and 82 cases in Toronto, Ontario, Canada. For this same time interval the median for Rochester was 7; Syracuse, 11; Buffalo, 13; and Toronto, 36. During this time the relatively low incidence of infantile paralysis in Rochester was repeatedly discussed although the recognized discrepancy was never explained.

On the basis of confirmed admissions to the Strong Memorial and Municipal Hospitals, the epidemic totaling 259 infantile paralysis patients began on May 25, 1944, and ended on December 28 of the same year. The incidence was thirty-seven times greater than the median for the past twenty-eight years.

The rapidly increasing number of cases in July and August revealed that the Strong Memorial and Municipal Hospitals combined under the School of Medicine were the only institutions which could provide the resources necessary for serving the community in this emergency, which was characterized by demand for care of patients during the acute and convalescent stages.

The difficulties thus suddenly created were more readily resolved because of the past two years of research under grant in aid from the National Foundation for Infantile Paralysis, Inc. During that time-interval a close correlation had been established for cooperation between the Department of Pediatrics, Department of Medicine, and the Division of Orthopaedics in the Department of Surgery.

Early in the emergency it became quite clear that the background of common interest thus created was a great advantage. Those responsible for making decisions were already aware of the need and able to agree upon an effective plan based upon known requirements dictated by the characteristics of infantile paralysis in the absence of specific treatment for the control of disabilities which follow in its wake.

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The plan was as follows: During the two weeks of isolation, the care of the patients was directed by the Department of Pediatrics, or the Department of Medicine in consultation, and with cooperation of the Division of Orthopaedics. All patients were transferred to the Orthopaedic Service at the end of two weeks after admission.

The latter service evaluated all patients on the basis of distribution and degree of muscle weakness or paralysis and determined the disposition, the duration, and the form of treatment to be given. Provision was made for following of these patients for a period of two years after the acute onset.

But, such an emergency demanded something more than beds, diagnosis and good treatment for patients. Simultaneously it was necessary to provide special resources in addition to those through which the hospital maintained contact with the community. Pertinent information regarding each patient was made available for parents, referring physicians, City and State Health Bureaus, social agencies, including daily reports to the hospital administration, and Visiting Nurses Association which provided trained personnel for the care of patients at home as directed by the hospital staff.

Muscle examinations were made within seventy-two hours following admission on all patients except when contraindicated by acute illness or local discomfort. At monthly intervals these examinations were repeated until the restoration of strength in weakened muscles returned to normal or reached a "plateau" beyond which there was no further improvement. A written monthly summary of each patient's progress was sent to those parents, the referring physicians, and those agencies interested either in the further treatment of the patients or in gathering information for the purpose of studying the epidemic as such.

All patients most severely disabled were hospitalized until they were physically independent with apparatus. After the acute and convalescent stages, patients who had residual muscle weakness were followed in a special clinic held once each week.

These were the practical resources developed by the dictation of an emergency which had no memorable likeness in this community in more than two decades. Precedents were not established by previous experience, but this was not so in the epidemic of 1945. The plan developed the previous summer required no significant modification, its application again proved effective in providing most for the patient, because the various relationships which the latter bore to the community and the state were properly considered as an essential part of treatment.

To some, it may appear that this broad base is too much to be practical in many places. How frequently it has been done is not known, but the indications for activating such a plan are defined by many factors. Without it patients may be treated effectively in the acute stage, but many parents are unnecessarily worried. The referring physician is uninformed as to progress and disposition and his relationship to parents and hospital become fouled. City and State Health Bureau statistics are exposed to inaccuracy, the services which they

are equipped to render to the community cannot be effective in such an emergency. Resulting partial or complete isolation of social agencies makes them unable to serve their respective functions. Visiting nurses do the best they can without supervision. In summary: the failure to provide for correlation of all these resources makes a difficult task more troublesome; moreover, it is safe to add that patients will not be as effectively treated during the convalescent and chronic stages of the disease when they most need direction for rehabilitation and protection from overexertion.

The requirements necessary for the correlation of the respective advantages rendered to infantile paralysis patients are common to most communities. Prevailing professional interest has financial support from the County Chapter of the National Foundation for Infantile Paralysis, Inc. Personnel is thereby available to execute the plan which provides for the most effective application of professional and community resources to the interest of all patients during and after the emergency created by a severe epidemic.

THE ROLE OF PHYSICAL MEDICINE IN POLIOMYELITIS

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THE intelligent care of the aftereffects of poliomyelitis is based on the premise that the extent to which a patient's functional capacity is ultimately restored is not dependent alone on the actual number of nerve cells destroyed during the acute stage of the disease, but also on the effectiveness with which the remaining cells can be put to use. In this over-all program of rehabilitation, it is the role of physical medicine to achieve three objectives:

1. To salvage all neuromuscular units left anatomically intact after invasion of the nervous system by the virus and to train these units to function with the highest possible coordination.

2. To prevent or minimize any musculoskeletal deformity that would handicap the most efficient use of these remaining neuromuscular units or render any indicated orthopedic apparatus or surgical procedure less effective.

3. To establish patterns of functional motion that will insure the most effective use of any necessary orthopedic apparatus and the maximum value from any necessary orthopedic procedure.

To appreciate fully this responsibility of physical medicine requires a complete understanding of the over-all program of care. Careful study of the various programs of care in use today reveals an amazing uniformity of approach in their attempt to achieve maximum rehabilitation. Almost all programs proceed in orderly progression through seven blocks or steps of treatment. These steps are summarized in Fig. 1.

If we appreciate the purpose of each step, we realize that the ultimate functional capacity regained by the patient is largely determined by the ability of the attending medical staff to complete each step thoroughly before undertaking the following one. There is now, as there has always been in the past, great controversy over specific routines and techniques in the over-all program. This controversy is of great value and will, and should, continue until we know a great deal more than we do now about the pathology of acute anterior poliomyelitis and the physiology of muscles and nerves. Perhaps when all these facts are known, a single method, complete in all its details and acceptable to all experienced investigators, can be formulated.

STEP I: SAVE PATIENT'S LIFE

It may seem unnecessary to indicate that the program of rehabilitation begins by first saving the patient's life. However, it is well to keep in mind that poliomyelitis is a potential danger to life during the first few days of the acute stage. Treatment during this stage is intelligent, supportive medical and

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nursing care, with the attending personnel on the alert to recognize and care for the first evidence of any emergency that might endanger the patient's life. The application of any form of physical therapy not consistent with this plan must not be permitted. It is not unusual to find patients with hot packs applied from head to toes at a time when that patient is fighting for his life to breathe against an accumulation of mucus in his throat and the added weight of hot packs on his chest.

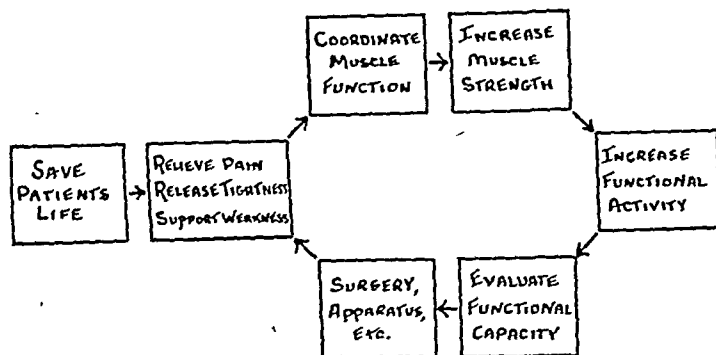


Fig. 1.

On the other hand, the judicious use of such physical agents as moist heat and passive motion may be indicated to relieve muscle tenseness and pain and thus allow the patient to rest more easily. Moist heat and gentle passive motion applied to the group of posterior neck muscles when the head is held retracted by spasm in these muscles may facilitate swallowing and breathing. In those patients where spasm and pain in the intercostal, abdominal, and back muscles are limiting breathing, careful attention to position and application of moist heat and gentle movement may be of almost specific value. It should be thoroughly understood that the application of any physical agent must be used with caution and should be specifically prescribed for each patient consistent with good medical judgment.

STEP II: RELIEVE PAIN, RELEASE TIGHTNESS, SUPPORT WEAKNESS

It is with Step II that our program of aftercare really begins. The purpose of this step is to prepare the patient for the initiation of voluntary motion. It should be readily appreciated that coordinated action of muscle groups acting on any bodily segment is impossible if motion of that segment is limited by pain and/or by limitation of joint motion. It is a basic principle of muscle re-education that restoration of effective use of muscles cannot be obtained and should not be attempted until a painless range of passive motion is possible in all segments upon which the involved muscles act. The relief of pain and release of all tightness in muscle and joint is thus the first step in muscle re-education. Until this is done, we can never fully regain the maximum use of the remaining skeletal muscles. The relief of pain and the release of tightness are accomplished by time, plus the use of intelligently prescribed sedatives, heat, and passive

motion. As in the use of all therapeutic agents, the type and frequency of application of heat and motion depend on the reaction of the patient. The immediate goal is painless passive mobility. There is no magical formula to achieve this end by physical medicine except in the intelligence and responsibility of the attending medical personnel.

It is also in this step that we begin our endeavor to prevent musculoskeletal deformities. Deformities (except for atrophy and weakness which are surely deformities but in the main not preventable) have just one cause: persistent faulty alignment of bodily segments which result in distortion of bones and joints and fibrous contractures of muscular and ligamentous tissue. In the early convalescent stage of poliomyelitis, such malalignment results from persistent, faulty posture in bed, caused by such factors as pain, muscle weakness, faulty beds, and the weight of bed clothes resting on the weakened extremities. Therefore, it is of utmost importance not only to preserve normal bodily mechanics and alignment by the early restoration of mobility in muscle and joint as mentioned, but also to prevent persistent faulty posture by the most effective methods possible. An effective support is not only one which holds the segments in proper position, but also one which in no way interferes with the other components of early care. It should be quite evident that the type of support will depend on the quality of available medical supervision. If little adequate medical supervision is available, a bivalved plaster cast is more effective than pillows or sandbags. Under intelligent supervision, an orthopedic bed, a footboard, and properly placed pillows are all the actual equipment needed to prevent deformities. Rigid supports are a poor compromise for good care.

STEP III: COORDINATE MUSCLE FUNCTION

Step III is probably the most important and certainly the most difficult step in the entire program. It is in this step that physical medicine in poliomyelitis justifies its existence. It is in this step that physical medicine has made its greatest strides in the treatment of poliomyelitis, not because any outstanding discoveries have been made in functional anatomy or bodily mechanics, but primarily because physical medicine has been given an opportunity to use its skill on bodily segments properly prepared for muscle re-education. It is obvious that the success of this step is absolutely dependent on the thoroughness with which the painless and complete mobility of the segment has been restored. The purpose of Step III is to train the patient to use every available muscle fiber with the greatest possible efficiency. It is a continued source of amazement and gratification to see the extent of functional capacity that can be developed by patients with very little muscle power but highly developed coordination. It must be stressed that coordination and power are not the same. Power without coordination may be disastrous to the patient recovering from poliomyelitis. Experience has taught us that all muscles in the involved segment do not recover with the same speed. The rate of recovery of an individual muscle group is not solely dependent on the physiologic state of the motor neuron but is influenced by many intrinsic and extrinsic factors too detailed to mention here. If, as

each of these individual muscles come under voluntary control, no attempt is made to coordinate their use, faulty habit patterns of motion will be built up by the patient through the use of these stronger and more easily available groups to the total exclusion of the weaker and thus less available groups.

The development of a truly high degree of coordination in the patient with moderate to severe involvement demands the attendance of a highly skilled physical therapist. Not all physical therapists, regardless of intelligence and training, have the qualities of personality, patience, and meticulous attention to detail so essential to good muscle re-education.

FRACTIONAL STRENGTH		
GLUTEUS MAXIMUS		N
ILIO PSOAS		N
SARTORIUS		N
TENSOR FASCIAE LATAE		N
HIP ABDUCTORS		N
HIP ABDUCTORS		N
INWARD ROTATORS		N-
OUTWARD ROTATORS		N
QUADRICEPS		N
HAMSTRINGS	INNER	N-
	OUTER	N-
GASTROCNEMIUS		N
ANTERIOR TIBIAL		N
POSTERIOR TIBIAL		F
PERONEALS		N
EXTENSOR LONGUS DIGITORUM		G
EXTENSOR BREVIS DIGITORUM		F+
EXTENSOR PROPRIUS HALLUCIS		G+
FLEXOR LONGUS DIGITORUM		G+
FLEXOR BREVIS DIGITORUM		N
FLEXOR LUMBRICALES		N
FLEXOR LONGUS HALLUCIS		N
FLEXOR BREVIS HALLUCIS		N

Fig. 2.

It is possible to determine the quality of the physical treatment carried out on an individual case by simply studying the functional muscle test rating of that patient. A difference of over 15 to 20 per cent in the functional rating of antagonistic muscles means one of two things: either that the early treatment was at fault and the purposes outlined in Step II were ignored, thus making good muscle re-education impossible, or that the program of muscle re-education was neglected or faulty.

Rarely a patient may be so inherently incoordinate that even the finest technician fails to attain proper muscle use. Examination of Fig. 2 reveals marked unbalance between the strength of flexors and extensors. This patient

was immobilized in a plaster cast for six months and then permitted rapid resumption of activity without supervision or guidance. If we simply recall our neuroanatomy of the spinal cord, we can readily see that such spotty involvement of muscles in each individual segment cannot possibly be the result

TRANSVERSALIS	8/14/43	10/30/43	1/3/44
GLUTEUS MAXIMUS	O	P+	F
ILIO PSOAS	O	P	P+
SARTORIUS	P	P+	P+
TENSOR FASCIAE LATAE	O	P	P+
HIP ABDUCTORS	Tr.	P+	F
HIP ABDUCTORS	P	P	P+
INWARD ROTATORS	O	P	P+
OUTWARD ROTATORS	O	P+	F
QUADRICEPS	Tr.	P+	F+
HAMSTRINGS INNER	O	P+	P+
" OUTER	O	P-	P+
GASTROCNEMIUS	Tr.	P-	P+
ANTERIOR TIBIAL	P	F	F+
POSTERIOR TIBIAL	P+	F+	F+
PERONEALS	O	P	P+
EXTENSOR LONGUS DIGITORUM	O	Tr.	P+
EXTENSOR BREVIS DIGITORUM	O	P	F
EXTENSOR PROPRIUS HALLUCIS	O	P+	F
FLEXOR LONGUS DIGITORUM	O	Tr.	F
FLEXOR BREVIS DIGITORUM	O	Tr.	P+
FLEXOR LUMBRICALES	O	Tr.	P+
FLEXOR LONGUS HALLUCIS	O	Tr.	P+
FLEXOR BREVIS HALLUCIS	O	Tr.	P+

Fig. 3.

of poliomyelitis directly but is due to haphazard motion and development of faulty habit patterns during the convalescent period. In Fig. 3 is shown the diffuse and balanced return of strength that follows adequate convalescent care.

STEP IV: INCREASE MUSCLE STRENGTH AND

STEP V: INCREASE FUNCTIONAL ACTIVITY

Steps IV and V are taken almost simultaneously. The increase of strength is obtained by carefully graduated activity, and increased activity further increases strength. While these steps are of the greatest importance to the patient, they are almost an anticlimax to the specialist in physical medicine. Actually, once the goal of maximum coordination has been reached and efficient habit patterns of motion deeply grooved, the patient's activities are limited only by his strength and endurance. I say this with full appreciation of the danger

of developing musculoskeletal deformities from faulty bodily alignment or mechanics during activity. As long as the patient remains coordinated, there can be no faulty bodily alignment or mechanics, unless the activity attempted is beyond the strength of the muscles called into action. It thus becomes the duty of the physician in charge of that patient's care to prescribe activity consistent with the ability of the patient to perform the activity and remain coordinated.

If a certain activity, walking, for example, is indicated, it must be determined if the patient can walk and still retain coordinate muscle action. If, in order to walk, a patient must resort to faulty bodily mechanics such as locking the knee in hyperextension or twisting the trunk in an unsightly manner, then walking must either be stopped or adequate assistive or supportive apparatus provided to enable the patient to carry out that activity in as nearly normal a manner as possible and with the correct coordination of muscle action.



Fig. 4.

More specifically, suppose a patient has weak dorsiflexors of the feet. If walking is attempted, an abnormal gait will result from the necessity to raise the weakened foot by excessive hip and knee flexion to keep the foot from dragging on the floor. In this case, a foot-drop support (Fig. 4), and there many simple and efficient ones, will hold the foot in correct position and allow normal mechanics of hip and knee in walking.

An overhead spring sling for a weakened shoulder girdle is probably the best example of truly assistive apparatus (Fig. 5). With this apparatus, the

arm is abducted to an angle where efficient motion of the shoulder girdle can be obtained and weakened muscles (deltoid, rotators, serratus magnus, etc.) are put in a position to act functionally and coordinately with but a fraction of their normal strength. Correct use without strain is encouraged and, with use, increased strength can be expected.



FIG. 5.

STEP VI. EVALUATE FUNCTIONAL CAPACITY

Eventually we come to a point in the program of convalescent care when we have done as much as we feel can be done by muscle re-education and graduated activity. In the mild case, this might have required but a few weeks; in the severe cases, perhaps several years. It is then that we carefully evaluate the patient's functional capacity in terms of that patient's ability to take his place in a normal environment. We want to know what that patient can do safely and practically. If his functional capacity is such that he can return to a happy and effective life, our program is complete. If, on the other

hand, his functional capacity is limited, we must determine if there is anything else that we can do. This necessitates a seventh step.

STEP VII: SURGERY, APPARATUS, ETC.

Step VII is a step of reconstruction and compromise. If an adequate program as outlined in Steps II through VI has been carried out, and the patient is still incapable of safe and practical locomotion, some reconstruction of normal musculoskeletal relationship or some compromise of normal coordination of muscle groups may enable the patient to achieve an independence of action otherwise not possible. The means to be considered are orthopedic surgery, the use of special apparatus, the development of trick movements, and the guided use of muscle substitution.

The results obtained by the orthopedic surgeon depend on the thoroughness of the conservative care during the period of convalescence. Certainly, if normal skeletal alignment and joint mobility have been preserved, the surgeon can do his work more efficiently.

To obtain the maximum value from orthopedic surgical procedures, post-operative care should revert back to Step II in the over-all program of care and proceed through Step VI for re-evaluation (Fig. 1). Patients may be taken through these steps of treatment many times before greatest possible functional capacity has been restored.

The training of patients in the use of trick movements and muscle substitution to increase functional capacity is a highly specialized phase of physical medicine.

SUMMARY

Physical medicine has an important and well-defined role in the treatment of poliomyelitis. It can be considered to have fulfilled its responsibility in the over-all program of care if:

1. All available neuromuscular units have been trained to function with the highest possible coordination.
2. All deformities that would limit the most efficient bodily mechanics have been prevented or minimized in so far as possible.
3. The most effective use of any necessary orthopedic apparatus or surgical procedure has been obtained.

understand every bit of medical conversation, but almost none of them are mature enough to force the medical staff to deal with their anxieties.

The situation does not lend itself to any easy solution. The superb skill of orthopedists in dealing with the deficits in the anterior horn cells and resulting disabilities is recognized. Most of the orthopedic thinking is based on the simple process of subtraction. So many units are gone, so many were there to start with. The sum is mathematically calculated and steps are taken to exploit the remainder.

If, however, the problem is not so easily stated or so readily solved a new approach is justified. It seems to us clear that there are genuine though perhaps not permanent intellectual deviations in certain cases. In all cases the management of the children is different from that of adults.

During the stay in the hospital the younger group suffer from absence of activity and almost certainly from absence of the warmth of affection which they should be having. All children are almost certainly subjected to anxieties which are not readily or automatically resolved.

After discharge other problems arise and seem to call for proper guidance from the psychologic point of view.

It seems important to mention the emotional disturbances caused in children who, back in their own circle, find themselves unable to compete socially, either by the nature of their physical handicap itself or by their parents' increased anxieties, and by necessity for rest, exercises, and the like. In other cases the parents' attitude seems to lead in an opposite direction. The child is urged to compete and to overlook his own difficulties. In other instances the child's reaction to regained freedom of activity leads to abnormal aggressiveness and exuberance.

The material which we have collected suggests that a serious effort should be made to protect these children from as many of the consequences of the disease as possible. The role of psychologic appraisal has been suggested. The method of instruction of children, parents, and teachers is so dependent on the personnel of the hospital that it is impossible to lay down rules, but it seems clear that mental and emotional difficulties are just as real a handicap to certain children as the paralysis is to others.

It is our impression that the inclusion of psychologic study is a reasonable and probably an essential part of the management of infantile paralysis. We are quite aware that behavior does not depend upon intellectual equipment alone, and we are equally sure that no hospital management can prevent all emotional difficulties.

It is quite evident, however, that almost every case of infantile paralysis will be cared for in hospitals during the acute stage and in specialized clinics later. What is done or not done in hospitals is of enormous importance. If by subjecting hospital procedure to review we can help the victims of infantile paralysis to make the transition from immobilization to activity and from the hospital to home and school with minimal difficulty, we need to appraise the intellect and consider the emotions and keep close contact with parents and child.

CHILD WELFARE WORK IN BRAZIL

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WHEN Dr. Martmer asked me to discuss child welfare work in Brazil, several things came to my mind as I sat thinking of the possibilities. First, how interested would a group of American pediatricians be in Brazil? Having just recently returned from two and one-half years in Brazil, it has been my observation that there are not very many people in the United States who are particularly interested in Brazil, or any other Latin-American country as far as that is concerned. Physicians as a group are rather adventuresome and always appear to be interested in new things and new experiences. After all, physicians are always seeking new knowledge, they are curious people by training, and one sees the *National Geographic Magazine* in many waiting rooms. Maybe you would bear with me on a sort of travelogue.

I also anticipated a question, "What on earth were you doing in Brazil?" I think that probably every person whom I have encountered has asked me that question. Therefore, as an introduction to some of the health problems in this great country to the south of us, I shall attempt to give a brief over-all picture of Brazil and an explanation of how an Army Medical Corps officer happened to be assigned down there.

It is impossible to discuss the health problems of Brazil without delving into its geography, civilization, economy, politics, and what not. This is true of any country as far as that is concerned, because the standard of living, the level of education, and the willingness of politicians to support health progress are the determining factors in how great the advance may be.

Sometimes before the United States was plunged into war, it was recognized by our political leaders that it would be to our advantage to have our Latin-American neighbors as friends. We had not paid much attention to them since the last war, but certain European powers had. These powers were making a great effort to control the trade of South and Central America. It was also true that Latin America looked to Europe and particularly France and Germany for cultural and scientific leadership, just as we had done some years before. These conditions helped to cement friendships. With a view then to trying to improve our own position, the so-called Good Neighbor Policy was inaugurated. Through fair trade treaties and loans to assist in economic development during the prewar years, we found ourselves in a fair position as far as our neighbors were concerned when war actually confronted us.

Shortly after Pearl Harbor, in January, 1942, the Foreign Ministers of the various American Republics gathered in Rio de Janeiro to discuss the defense of the Western Hemisphere and ways in which all could cooperate in the prosecution of the war against the Axis. None of these countries had large armies or

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navies and it was therefore evident that the United States would have to undertake most of this defense. There were thousands of miles of coast line that had to be protected, and many more thousands of miles of sea lanes that had to be kept open. In 1942 the Germans and Italians were running over North Africa and even attacks on South America were feared. With Axis bases in South America we could not have defended the Panama Canal, and even defense of the United States would have been difficult. Furthermore, we had to develop supply lines to Africa and Europe and protect them. We were granted the privilege of establishing bases as we needed them throughout Central and South America to carry out these objectives. The large bases in Brazil formed the main supply line for the early fighting in North Africa and later were links in the air line that extended to India and China. Active submarine patrols and the escorting of convoys were also carried on from those bases.

Probably of as great importance as the bases were certain strategic materials that were obtained from some of these countries. We in the United States have always been very self-sufficient people. We were the "Arsenal of Democracy," we possessed the "know how" and ability to produce great quantities of supplies. We produced more steel than the rest of the world combined and thus more machinery of war. But, to produce steel one must have manganese. There is little manganese in the United States, and practically all we used had to be brought in from the outside. This was one of the very important items obtained from Brazil. To make guns, bombs, and planes, machine tools were necessary. To make machine tools industrial diamonds were needed and these came from Brazil. For the thousands of radio and radar sets used on ships and planes, quartz and mica were needed. We had very little and normally our chief source of supply was India, which was then cut off from us. These minerals were so critically needed that a large air transport service flew them from Brazil to the United States. There were many other items, perhaps not so critical, such as vegetable oils, hemp products, rubber, cinchona, iron, copper, nitrates, and tin that were imported in huge quantities. In fact, our importation of these products went up about five hundred per cent during the war period.

As many of these industries had not been very highly developed, one of the big problems was to devise ways and means of increasing the production to meet the demands. It was necessary to develop mines and transportation facilities and to furnish technicians to operate them. Large labor forces had to be recruited, and in one instance 65,000 people were moved on one project. Most of these operations were located in frontier territory. Disease was the chief factor in keeping people from work. In many areas it was not unusual to find 75 per cent of the people with chronic malaria, and in addition hookworm, the dysenteries, and typhoid fever were rampant. It was impossible for these people to do a day's work or even a good hour of hard labor a day.

To combat this combined problem of protecting the health of our troops and the people engaged in procuring these critical materials, a public health program was inaugurated as a cooperative endeavor. The Brazilian Ministry of Health

and the Institute of Inter-American Affairs supplied funds and personnel to conduct the program. Army physicians, sanitary engineers, and other technicians were assigned to the Institute of Inter-American Affairs to supervise and carry out this work. This special health service was responsible for the health work and medical care in the areas adjacent to bases, the mining regions in Central Brazil, and the vast rubber and vegetable oil producing Amazon Valley. The entire area involved was larger than that of the United States and was mostly rural and undeveloped. It was to this work that I was assigned, which was of a general public health character, as you can see. It was all part of a coordinated political, military, and economic program to further the cause of the Allies.

In order to comprehend the necessity for the creation of such a health program one must understand the problems as they existed in Brazil at the beginning of the war. Brazil has probably advanced more than any other Latin-American country in its medical education and in its public health services. Though Brazil is not a highly industrialized nation it is developing rapidly in this direction in a few sections of the country. The same might be said of education in general, living conditions, and other criteria of an advanced civilization. The result has been the creation of a country with very glaring contrasts. The large population centers of Rio de Janeiro, São Paulo, Belo Horizonte, Porto Alegre, and a few others are highly developed, modern cities with most of the advantages of our cities. Yet in the smaller communities and rural areas there has been little progress and there are few modern advantages.

The health and medical work has been well developed in these larger centers along with the other modern refinements, but it has lagged greatly in the less populous areas. Brazil being a very large country with not too great a national income, the rather natural and logical course has been followed to make improvements and advances where the largest number of people would be affected. Our work was intended then to augment and supplement the work that was already being done by the existing National and State Health Departments, and particular care was taken to avoid duplication of effort. As the Army and Navy bases, as well as the vast mining and rubber areas, were located mostly in the less developed regions which did not have well evolved health programs, the task fell to our lot of formulating and executing a very basic health program.

Our first undertaking, naturally, was to familiarize ourselves with the health problems in the areas for which we were to be responsible. This necessitated a study of the country, its geography, climate, population distribution and trends, vital statistics, industries, food supply, and living conditions, as well as surveys of the health conditions and the existing medical and health facilities.

As already mentioned Brazil has advanced greatly in its medical education. There are a half dozen good medical schools and several others that are not bad. About two-fifths of the physicians south of the United States are located in Brazil which contains about one-third of the population of Latin America. Roughly there are 20,000 physicians for 45 million people in that country, or one physician for every 2,500 people. The same dislocation exists in Brazil as in the United States, only to a greater extent, in that most of the physicians are

located in the large cities and very few are located in the less developed regions. The same applies to the activities of the National and State Health Departments, as I have already explained.

In the metropolitan areas the various medical specialties are well taken care of, and fairly good medical care is available either through the private practitioners or public clinics.

The preventive medical work of the country is directed by the National Health Department. This department handles more or less special problems that are nationwide in scope. Many special services have been developed that have done outstanding work.

Yellow fever, which once was a great scourge, has been practically eliminated, and a very active campaign of vaccination against yellow fever is still carried on.

Some of the finest antimalaria work in the world has been done in Brazil. The campaign in the Northeast against the Gambia mosquito, which was conducted in cooperation with the Rockefeller Foundation, was probably the outstanding antimalaria campaign in all medical history. One need not worry about acquiring malaria in the larger cities. The vast interior is so extensive and the problem is so complicated that it has been a very great undertaking on a nationwide scale.

A leprosy service that has made a fine record is maintained by the National Health Department. Probably the best leprosy work in the world has been done in Brazil. Fine leprosariums have been established for the segregation of infectious cases. Early diagnosis clinics and also places where contacts can have routine examinations are operated throughout the country. A private agency for protection against leprosy has provided a chain of preventoriums where children of lepers may be placed for protection and observation.

There is a tuberculosis service that is becoming more active all the time. The tuberculosis problem is very great as I shall attempt to show later on. For Brazil to try to institutionalize active cases as we have done would be financially impossible. There are a fairly large number of tuberculosis hospitals into which the patients with the more advanced cases ultimately go, and more of these hospitals are being planned all the time. However they are attacking the problem through early diagnosis and ambulatory collapse therapy. Centers have been developed in all metropolitan areas where examination, including x-ray, is available. Mobile units are constantly being increased so that outlying districts can be reached with these early diagnosis campaigns. The micro-x-ray technique was developed in Brazil and is used extensively. These small pictures reduce the cost of x-rays considerably.

Lack of public health nurses has made effective home visits impossible, so that really active case finding and follow-up work cannot be done. In one small town I am familiar with, out of the 40,000 population, 27,000 had been x-rayed during the past two years. In these same centers and mobile units there are facilities for giving pneumothoraces, and this is the principal means of treatment and of reducing infectivity. In this one city just mentioned, they did 17,000 pneumothoraces during the same two-year period.

There is still the great problem of poverty among so many of the people, which for some time to come will retard any antituberculosis program. One cannot help but feel, however, that Brazil is on the way to developing a good antituberculosis campaign.

There is also maintained a service of BCG. This was started as a private endowed organization seventeen years ago. It is now semiofficial and receives some government support. They prepare their own vaccine and provide facilities for the vaccination of all newborn infants. This service is large enough to reach practically all in the larger cities, but it is carried out through the local health agencies in small communities where the service may be inadequate or lacking entirely.

This vaccination program against tuberculosis was very interesting to me, as it is probably the largest program of its kind in the world today. It was started in 1927 and just recently a seventeen-year report was made by its director, Dr. Arlindo de Assis. The vaccine is made from cultures obtained from the laboratory of Prof. Calmette in Paris and is carefully prepared and checked. Calmette's original technique has been changed gradually until now they use a live culture vaccine of fourteen days' growth instead of the usual twenty-five-day growth. The dose has been increased from 3 cg. to from 9 to 20 cg. orally. Revaccination after varying periods of time is practiced and also the vaccination of older children and young adults where they are anallergic. At first only those in contact with tuberculosis were vaccinated, but now the vaccination of all newborn infants is attempted.

During these seventeen years there have been 161,152 newborn infants vaccinated in Rio de Janeiro. At this rate more than one-half of the registered newborn infants in Rio are now being vaccinated.

Outside of Rio about 180,000 other newborn babies have been vaccinated making a grand total of around 340,000 infants receiving BCG.

A control experiment has been carried on in Rio for five years. There are 1,426 families under observation where active tuberculosis has been verified, usually in the parents. In this group of families 2,050 children were vaccinated with BCG at birth and 2,598 children were not vaccinated. These children were usually brothers or sisters and are living together with the siblings with active cases.

After five years of observation in this group, Dr. de Assis makes the following statement:

"In the vaccinated group, tuberculosis occurred in 20.8 per cent and was usually benign in character. Death from tuberculosis occurred in 2.1 per cent.

"In the unvaccinated group, tuberculosis occurred in 39.6 per cent and death occurred in 13.2 per cent."

I am not certain just what the diagnosis of tuberculosis was based on, but I am of the opinion that it was on the basis of demonstrable x-ray lesions. A positive tuberculin test was apparently not regarded as evidence of tuberculosis.

In addition to this control group over 41,000 other children have been under regular observation.

Brazilian physicians are practically all enthusiastic about BCG vaccination and it is assumed that it is without harm and that protection does occur.

I had many arguments over the pros and cons of allergy and immunity, and personally I am not convinced. It will take more time and better controls to tell the story. These families under observation are likely to take some other precautions learned of through contacts with the physicians and nurses. Also I suspect that a considerable number of the active cases were being given ambulatory treatment, which would tend to lessen the possibility of infecting others.

There is also a National Department of the Child. This department is organized somewhat like our Children's Bureau and carries on investigations, prepares information, and stimulates child welfare work generally. The annual budget is quite small, so it has not been able to develop to any considerable extent.

Throughout the country, each state maintains a health department with a full-time director of health. The State Health Department is responsible for all of the health activities in the state and supplies a limited number of personnel which are usually on a part-time basis. The necessary funds to carry out the health work and medical care for indigents in the various municipalities, which correspond to our counties, are also provided from the state health budget. The State Health Departments are also under the jurisdiction of the National Health Department. Here again the largest population centers receive the greatest benefits. The capitol cities all have health centers and the larger ones frequently have several. The health centers carry out the same type of programs as those in the United States and are gradually becoming a considerable force in many communities. What child welfare work is done is usually through these centers in the form of medical and preventive medical clinics. Probably the best general health work in Brazil is done through these centers.

There are two schools which offer one-year postgraduate courses in public health for physicians. These schools also conduct specialized courses in the various fields of public health such as child welfare, maternal welfare, tuberculosis, leprosy, epidemiology, statistics, and laboratory. A fair number of well-trained people are being prepared.

One of the greatest handicaps to reaching the masses on public health matters is the lack of public health nurses. With only about 175 public health nurses in the country, 135 of them are found in Rio de Janeiro, which is a city of 2 million people.

Very little health work has been done in the schools as we know it in the United States. In Rio and São Paulo where the health center programs are fairly well developed it has extended to the schools somewhat. Also in these cities the school lunch program is being developed. Recently a few private schools have employed nurses to supervise the health of the students. For all practical purposes the vast part of the country is without any school health program. The teaching of health subjects in the schools hardly exists.

There is one large private organization; the Legiao Brasileira de Assistencia which is supported by contributions and also partly by taxation, that engages

in welfare work, much of it directed toward children, orphanages, day nurseries in the larger cities, and an occasional children's hospital are operated by this group.

In all of Brazil there are approximately 1,300 hospitals containing 95,000 beds. This is about 2 beds for each 1,000 persons. Here again a great disparity is seen in that the larger cities may have 8 or 9 beds for each 1,000 people, while the smaller cities and rural areas have practically none. Most of these hospitals are operated either by the state or welfare societies in cooperation with the Catholic church. In the larger cities several fine, large hospitals have been completed in recent years. There are very few hospitals devoted exclusively to the care of children outside of Rio and São Paulo. Each of these large cities has two or more children's hospitals. I do not know how many hospital beds are available for pediatric cases.

Hospital care does not nearly approach our standards due chiefly to the lack of nursing care. In all of Brazil there have been only about 600 nurses graduated in the last 25 years. I believe there are now six recognized nursing schools in the country that can graduate less than 150 nurses each year. Most nursing care is given by attendants who are of the domestic servant level.

The resident and intern staff has never been developed in hospitals, so that patients are seen infrequently.

Most Brazilian physicians realize the shortcomings of their hospitals, but the present wage scale for nurses, which is under \$50 a month, and the tendency of the public to regard nursing as a menial work, are largely responsible for the failure to develop an adequate nursing profession. At the present rate of progress it will be many years before hospital care develops to a point that is anywhere near adequate.

There is a Pediatric Society in Brazil with about 70 members. Many of these men are very fine pediatricians by anyone's standards. Most of the older men were trained in Europe, usually in Germany or France. In more recent years there have been several trained in the United States. It is my belief that most young Brazilian physicians would prefer to do postgraduate study in the United States and with any kind of encouragement they would look to us for medical leadership.

In attempting to present some of the chief health problems of Brazil Charts 1-11 may help to illustrate the general situation.

After collecting such information and after making studies of our own it became very evident that the chief causes of illness and death were diseases that were community problems.

The dysentery and typhoid group of diseases causing almost 350 deaths per 100,000 population, tuberculosis almost 300, and pneumonia and influenza about 200. Such diseases as malaria and syphilis cause a sizeable number of deaths, around 30 a year each per 100,000 of population. Though malaria may not cause as many deaths directly, it is a great incapacitator and chronic malaria is frequently a contributory cause of death, many people suffering from it, being easy victims for the respiratory infections and the diarrheas.



BRAZIL POPULATION DENSITY 1940

POPULATION DENSITY
PER SQ. KM.

	LESS THAN ONE
□	1 TO 5
□	5 TO 10
□	10 TO 25
■	25 TO 50
■	50 TO 100
■	OVER 100

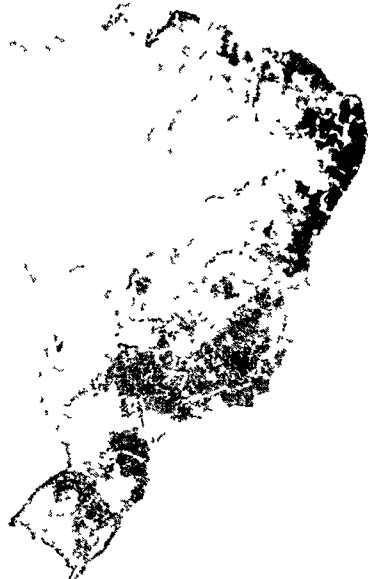


Chart 1.—Map of Brazil showing the distribution of population.

It will be noted that the greatest concentrations of people, 100 or over per square mile are located around Rio de Janeiro and São Paulo with the next most populous areas the States of Rio de Janeiro, São Paulo and the area around the tip of the bulge. It is estimated that 60 per cent of the population is within 100 miles of the coast.

Also a comparison of the size of the United States and Brazil can be shown. If the United States were superimposed on Brazil with Washington at Rio de Janeiro, the city of Natal on the tip of Brazil would be out in the middle of Hudson Bay. Belem on the mouth of the Amazon would fall near Helena, Montana, and Boa Vista on the Rio Branco would be at San Francisco. Benjamin Constant on the Peruvian Border would be about 700 miles off the coast of Lower California.

The greatest cause of infant deaths is also the dysentery group of diseases. Next are the acute respiratory infections and tuberculosis.

It is interesting to note that the infant death rate for the entire country was given as 185 per 1,000 live births in 1943. In Rio the rate was 150 and in São Paulo 115. In the cities along the northern coast the death rates for infants run from 235 to 450 per 1,000 live births. I have seen many areas where, from the best available information, the death rate for infants is around 500 per 1,000 live births. I really do not believe it is unusual in the vast interior of Brazil for people to lose at least one-half of their children.

It was very difficult to determine the prevalence of the various disease entities from what statistical information was available. It is only logical to

POPULATION DISTRIBUTION BY AGE AND SEX—1920

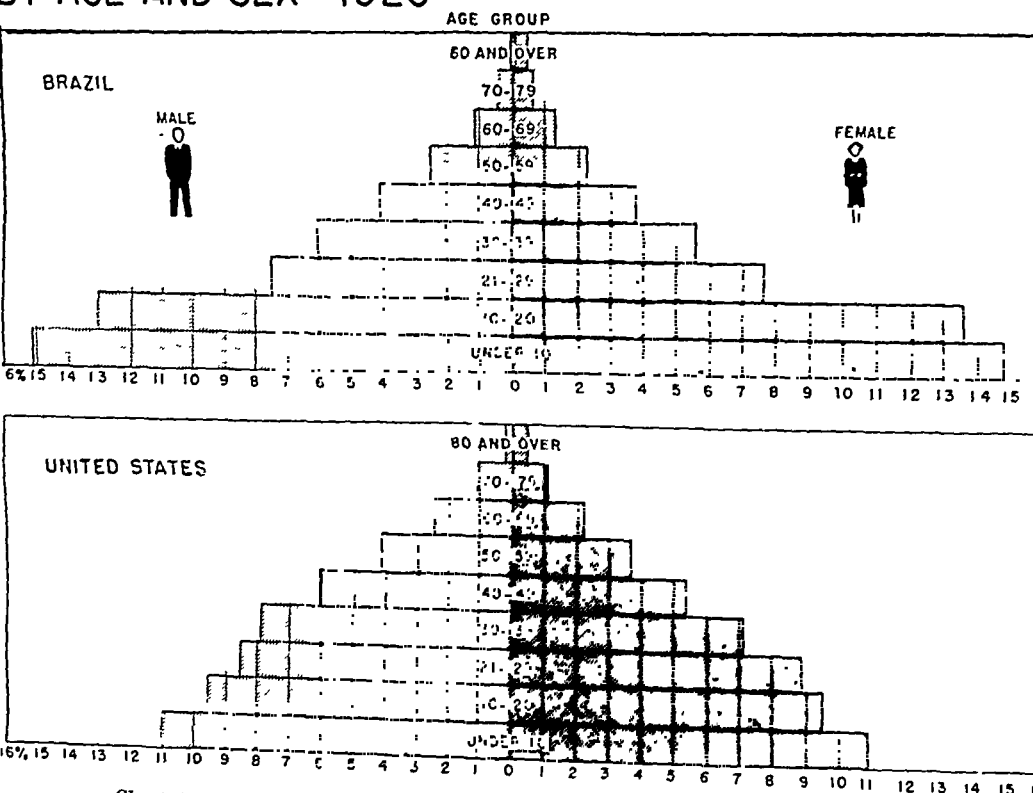


Chart 2.—Distribution of population by age and sex as compared with the United States.

It should be pointed out that it is difficult to interpret the existing statistics. In the well-developed areas where active health departments exist, the figures are fairly accurate, but in the larger part of the country statistics are incomplete and therefore do not always give a true picture of the conditions. It will be noted that the highest percentages in the young age groups make up a much greater percentage of the population in Brazil than in the United States. This percentage falls off abruptly at around 20 years. The terrifically high mortality rates in early life are a factor in this, plus probably an inaccurate census in the older age groups. As the collecting of statistics is relatively recent, the figures on the younger age groups are likely to be more accurate.

assume that where the death rate from intestinal diseases is 350 per 100,000 of population, that the morbidity figures would be very high, and of course actual experience bears this out. The same conclusion could be drawn from the figures on tuberculosis.

In the areas in which we worked, surveys were made to determine the incidence of certain prevalent diseases. Several places were found where infestations with intestinal parasites approached 100 per cent. Practically everyone had *Ascaris* and usually two or three varieties of lesser parasites such as whipworm or *Strongyloides*. I had never regarded these parasites as particularly harmful, but I had never seen really heavy infestations. I soon learned

TREND OF CRUDE BIRTH RATES Brazil and the United States

(LIVE BIRTHS PER 1,000 POPULATION)

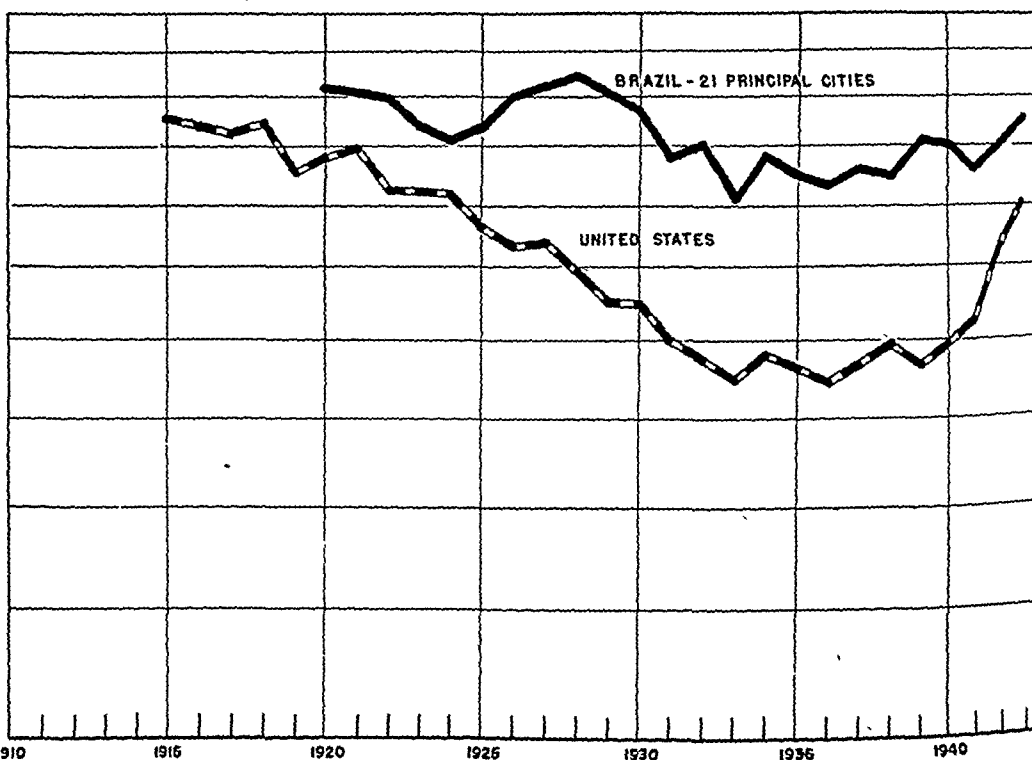


Chart 3.—Trend of the crude birth rates with a comparison of the rates in Brazil and the United States.

The Brazilian rate is consistently higher than that of the United States by 2 to 3 births per 1,000 of population and tends to be about stationary.

that several hundred *Ascaris* in one child, and especially when the diet was inadequate, could produce a profound malnutrition and anemia. These children were ready victims for any infection that might strike them. This is undoubtedly one of the factors in the high death rate from respiratory diseases.

Hookworm was particularly common, many surveys showing as high as 90 per cent positive stools. Hookworm is really a debilitating disease and particularly when the diet is poor. It is usually severe in children, but it also incapacitates many adults and prevents them from supporting themselves or their families.

Amebiasis is very common and is frequently seen in conjunction with the other parasites.

I should like very much to know the incidence of tuberculosis in Brazil. It is a very prevalent disease and causes 300 known deaths per 100,000 people each year. I strongly suspect that it causes many more than this. I have talked to

END OF CRUDE DEATH RATES Brazil and the United States

(DEATHS PER 1,000 POPULATION)

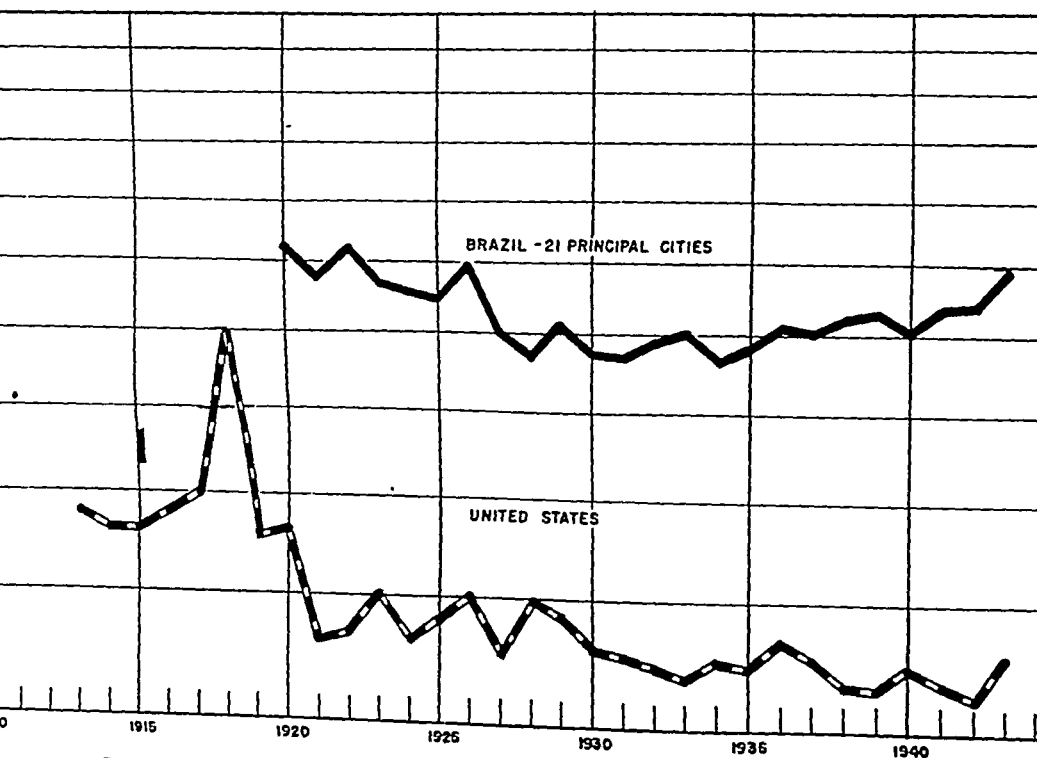


Chart 4.—Trend of the crude death rates—Brazil and the United States 1913-1943.

The Brazilian rate is at least twice that of the United States, averaging about 19 deaths per 1,000 as compared with an average of about 9 per 1,000 for the United States over this thirty-year period. The Brazilian rate has tended to go up in recent years and the United States rate is going down, being only about 7 in 1943. Part of the rise in the Brazilian rate may be due to better recording of deaths in recent years.

many men working on this problem and the lowest estimate was that 20 per cent of the population had tuberculosis. Others have given as high as 70 per cent as their guess. It is a very great problem and the country would be financially unable to attack this problem as we have done it in the United States. As I attempted to explain, while discussing the tuberculosis service, they are working hard within their means and seem to be making some progress.

Outside of the metropolitan areas, malaria is a dreaded disease. I have seen communities where 75 per cent of the people have had positive blood smears. For all practical purposes this means about 100 per cent infection. Such a community is barely able to exist. Few people can do much in the way of work and the death rate is very high, if not from malaria itself, from some intercurrent infection.

INFANT MORTALITY IN THE AMERICAS



Chart 6.—Map of North and South America showing the infant mortality rates.

Though we are discussing only Brazil it is interesting to see the over-all picture in Latin America which does not differ on the whole from that in Brazil.

circle, with many people ill and thus unable to work resulting in an even greater food deficit. Transportation facilities are such that it is difficult to provide a good food supply from outside sources.

I know you are all beginning to wonder where the child welfare part of this talk comes in. I have been attempting to show that the great health problems in Brazil are very basic problems. They are concerned with lack of education generally and regarding health matters in particular. Such things as the lack of safe water supplies, proper excreta disposal facilities, poor food handling, lack of cleanliness generally, poor eating habits and lack of food are all very basic environmental problems. These problems are also community problems.

END OF INFANT MORTALITY RATES BRAZIL and the United States

(DEATHS UNDER 1 YEAR PER 1,000 LIVE BIRTHS)

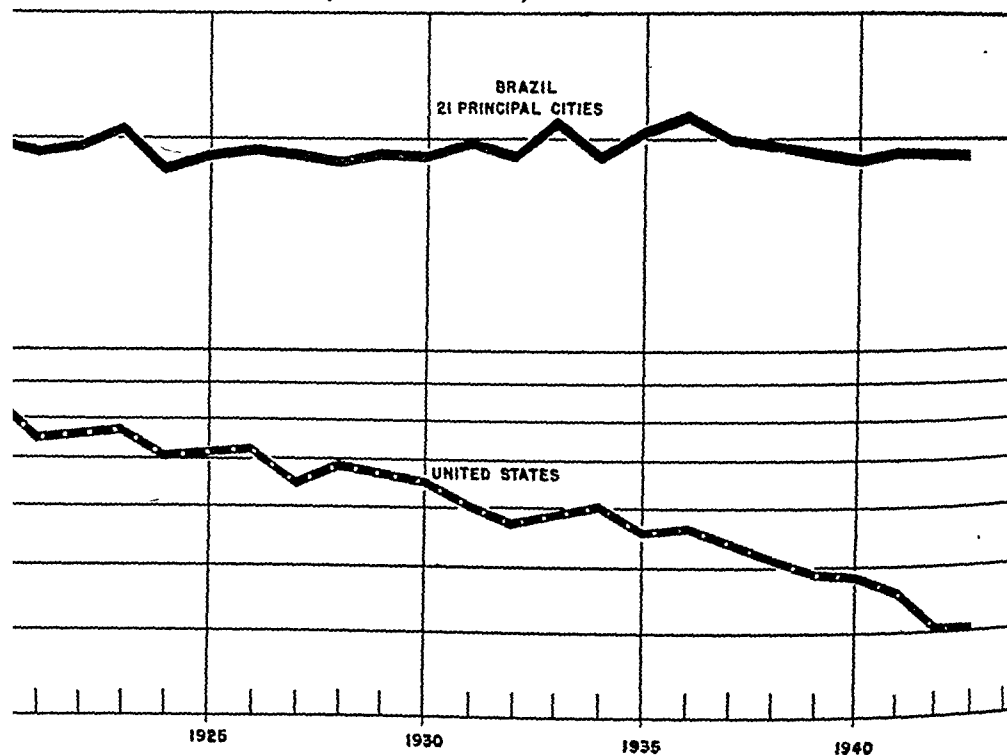


Chart 5.—Trend of infant mortality rates in Brazil and the United States.

The Brazilian rate has not changed over the twenty-three-year period covered, the rate being about 200 per 1,000 live births in 1920 and practically the same in 1943.

The very marked drop in the United States rate from 87 in 1920 to about 40 in 1943 is something we are very proud of and is a marked contrast to the Brazilian rate.

Generally in the interior, malnutrition is very prevalent and complicates the picture where other diseases are present. I never expected to see so many cases of nutritional edema and beri-beri. This situation is caused by lack of food primarily and also by poor eating habits due probably to many generations of an inadequate food supply. Rice and beans are the chief articles of diet and these are grown only in certain sections. Meat is scarce in great parts of the country and is very expensive when available. Milk can hardly be had except in the larger communities. Vegetables have never been grown in any quantity and most people have never learned to eat them. Even the fruits that are available are not used as extensively as they should be. Probably the worst dietary habit is the widespread use of farinha which is a meal prepared from the mandioca root. It is mostly cellulose, with little or no food value and is cheap. As it is filling, it has become one of the chief articles of the diet of the poorer people. These poor eating habits and the general lack of food cause a vicious

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TREND OF INFANT MORTALITY RATES BRAZIL and the United States

RATE (DEATHS UNDER 1 YEAR PER 1,000 LIVE BIRTHS)

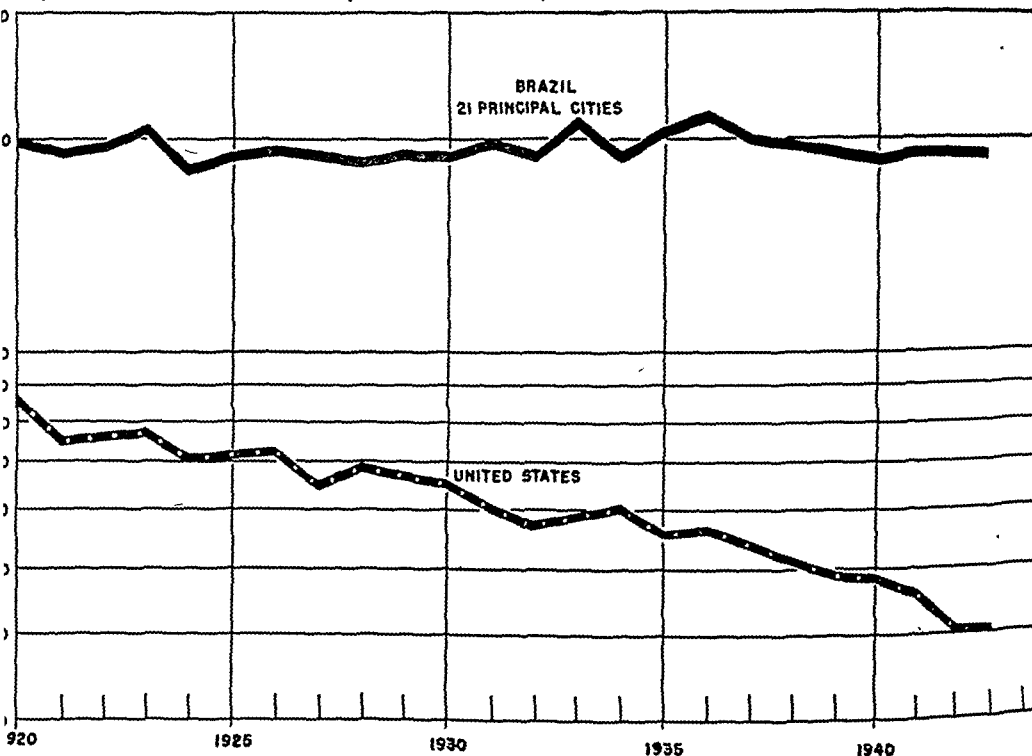


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LEADING CAUSES OF DEATH 1943

Brazil and the United States

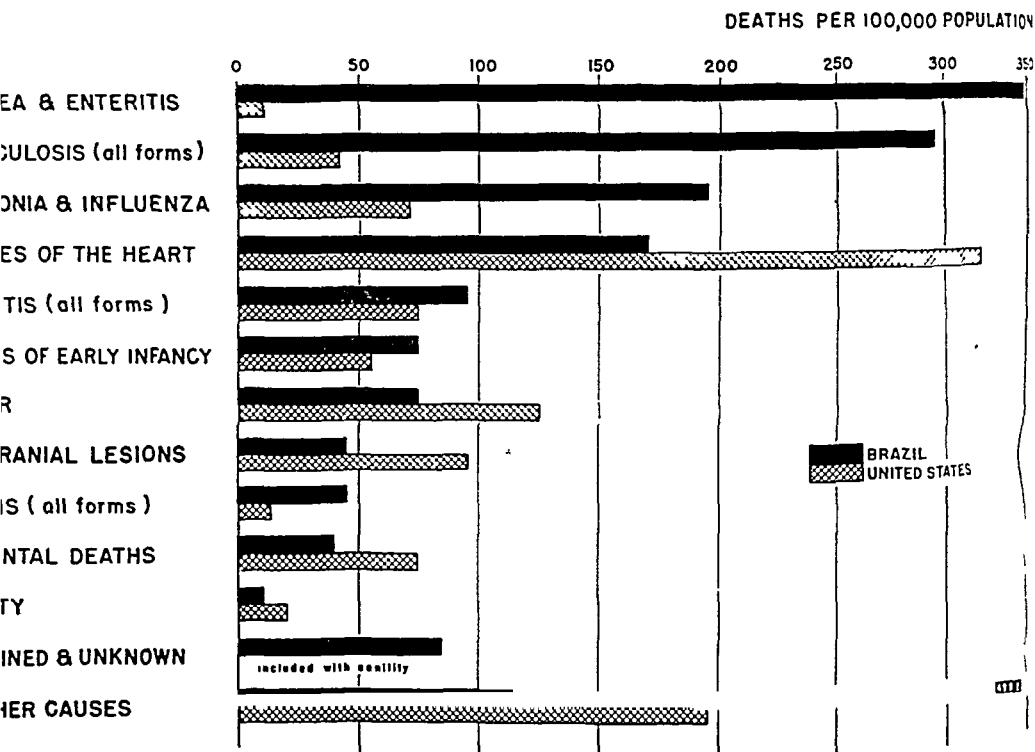


Chart 7.—Leading causes of death in Brazil and the United States. This chart brings out the very high death rates from the diarrheas and enteritis, tuberculosis, and respiratory infections.

Deaths from heart disease are not nearly as high in Brazil as in the United States. Part of this, no doubt, is due to the fact that more people live to an older age in the United States. Another factor is that rheumatic fever hardly exists in Brazil.

It is impossible to do much about safeguarding the child until the family and the community of families is protected and until the people are educated to the necessity for certain basic safeguards to their health. We in the United States take these basic health precautions as a matter of fact and have practically stopped talking about them. We are now putting on the frills and the lace, where in most Latin-American countries the very primary type of health work has to be done.

Even in the large and modern appearing cities of Rio and São Paulo, you will remember that the infant mortality rates are still 150 and 115, respectively, per 1,000 live births. Most of the childhood deaths throughout the country are caused by preventable diseases such as dysentery, tuberculosis, and syphilis. Many other deaths can be attributed to secondary diseases that are preventable. The only cure for such a situation is the education of the public and the

MORTALITY RATES IN RIO DE JANEIRO — 1930-1939

INFANT MORTALITY RATE

..... 180 Per 1000 Live Births

NEO-NATAL MORTALITY RATE

..... 50 Per 1000 Live Births

STILLBIRTHS

..... 90 Per 1000 Live Births

MATERNAL MORTALITY RATE

..... 9 Per 1000 Live Births

Chart 8.—Mortality rates in Rio de Janeiro.

CAUSES OF INFANT DEATHS IN RIO DE JANEIRO 1930-1939

	Under 1 Month	2-12 Months	Over 1 Year
Infectious Diseases	20%	19%	19%
Gastro-Intestinal	17%	50%	41%
Respiratory (including T. B.)	14%	21%	19%
Natal and Neo-Natal Causes	46%	3%	15%
ALL OTHERS	3%	7%	6%

Chart 9.—Causes of infant mortality in Rio de Janeiro, 1930-1939.

politicians. Unless people are informed of the dangers and how they can be prevented, and unless the politician and others in a position to lead the way realize the economic importance and the political value of health work, no great progress will be made.

Since our organization was charged with the responsibility of controlling disease conditions in strategic areas in the shortest time possible, of necessity we had to give our first attention to certain problems. In the Amazon and Rio Doce Valleys, the malaria problem was very great and was hindering the essential work to a considerable extent. This then received our first attention. With a handful of malaria experts and entomologists, mostly Brazilians, studies were started and field workers were trained to carry on the antimosquito work. A laboratory was established at Belem and ultimately studies were made of the entire Amazon and Rio Doce Valleys and the entire coastal region of Brazil.

DEATHS CAUSED BY INFECTIOUS DISEASES

	Under 1 Month	Under 1 Year
Congenital Syphilis	56 %	31 %
Tetanus	22 %	7 %
"Influenza"	13 %	27 %
Pertussis	3 %	10 %
Measles	1 %	6 %
OTHERS	5 %	18 %

Note that the dysenteries and the typhoid group of diseases are included under gastro-intestinal diseases.

Tuberculosis is included under respiratory diseases.

Chart 10.—Deaths caused by infectious diseases.

It must be remembered that on Chart 9, the dysenteries and the typhoid group of diseases are included under the gastrointestinal group, and that tuberculosis is included under the respiratory diseases.

In many instances control work of a permanent nature would have been far too costly, and in these places the disease was controlled fairly effectively by temporary measures. Whenever possible, plans were prepared for permanent work and presented to officials for use in longer term programs.

The health and medical care of 65,000 people who migrated into the Amazon Valley in 1943 was also placed in our hands. This included the examination and immunization of all at the different collecting stations. Of course poor risks were eliminated. While in transit and after being deposited in the Valley, keeping them in good health was our responsibility.

GENERAL MORTALITY IN THE AMERICAS

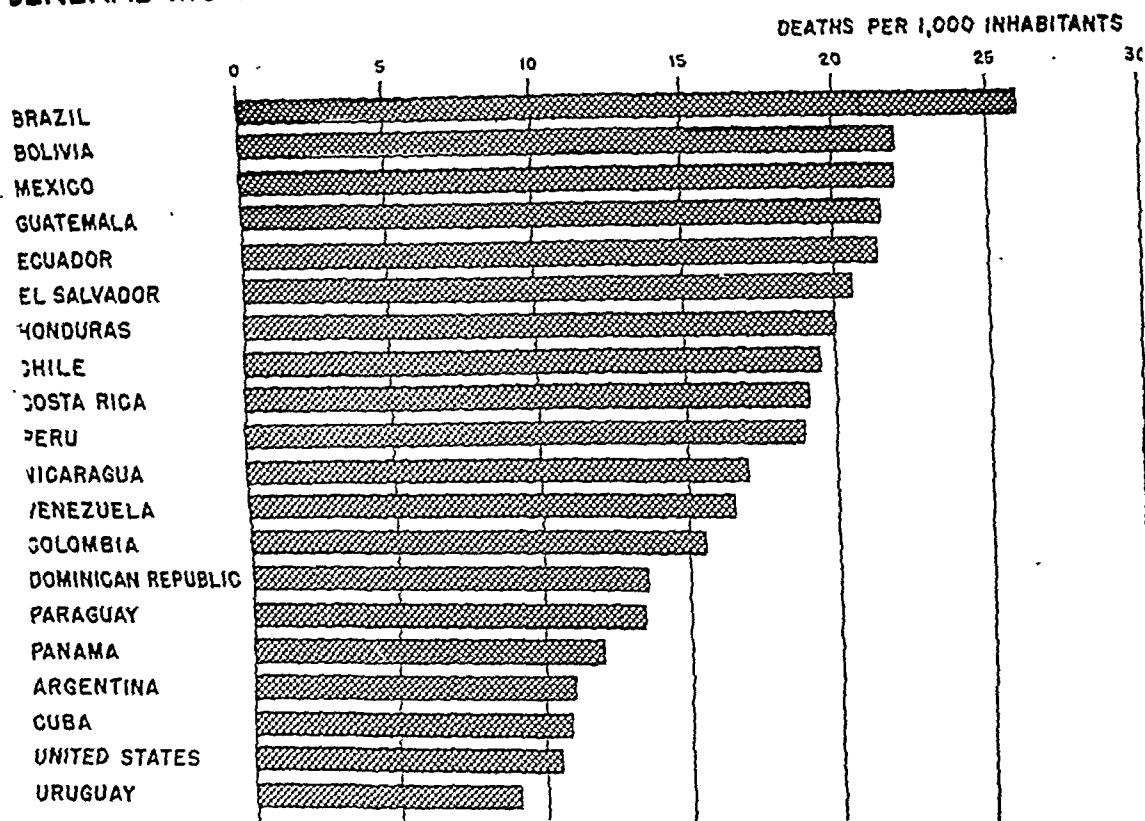


Chart 11.—General mortality in the Americas.

Aside from malaria, the great problems in the Amazon Valley and in the mining regions in Central Brazil, were dysentery, intestinal parasites, malnutrition, respiratory infections, and venereal diseases. We realized only too well that in order to control these diseases, longer term programs would have to be planned. We could help the hookworm situation for the time being by putting on treatment campaigns and likewise help to prevent dysentery to some extent by controlling and treating the water supplies and supervising food handling. However, these diseases are due to poor environmental sanitation and lack of education. Treating them alone was not sufficient. With the view in mind then of trying to effect permanent improvement and at the same time leave something in Brazil that could be carried on after our leaving, we prepared plans for a general basic public health program.

In order for such a program to be successful, certain trained personnel were essential. We were fortunate in acquiring a few Brazilian health workers who were well trained and most capable people. Four of them had graduated from public health schools in the United States. Training centers were established

in Belem for physicians and for field workers in malaria, and a health worker called a *visitadora*.

These *visitadoras* were to perform a job somewhat similar to that done by the public health nurse in the United States only in a limited way. They were to be home visitors and the missionaries to spread health education to the public.

Courses were given in several areas to schoolteachers to instruct them in the art of teaching health subjects to their pupils. Arrangements were also made with the school officials to have a certain period of time devoted to health education.

While this training program was going on, buildings were constructed or renovated to serve as small health centers in important communities. Projects were also being promoted with local officials to provide safe water and proper excreta disposal facilities in these same communities.

In our offices in Rio de Janeiro material was being prepared to carry on the health education program. As the people to be reached were mostly illiterate this material had to be very simple and chiefly visual in character. Charts, pictures, and posters were prepared for the use of the *visitadora* and the schools in their teaching. One of the most effective teaching aids was a film strip to be used as a series of slides. Along with this a recording was made to tell the proper story to go with the pictures. A great variety of subjects was covered in these film strips.

When I left Brazil in late August, thirty-five health centers were in operation. Each was staffed with from one to three physicians, several *visitadoras* and the necessary malaria field workers, sanitary inspectors and laboratory workers. These health centers served as a small health department and conducted campaigns against the prevalent diseases as well as a general health education program. Special clinics for children, expectant mothers, tuberculosis, venereal diseases and nutrition were developed. In areas where special problems existed, clinics were organized to handle these. In most of these places there were no other physicians, so that medical care also had to be given.

Safe water supplies and latrine projects were provided in these communities. In a few of the larger towns fairly extensive water and sewer systems were installed, usually on a cooperative basis with the municipality.

Providing and operating hospitals was avoided as much as possible. Hospitals are expensive to operate. Simply treating the diseases that were prevalent did not solve the problem. We felt that the money and work expended in preventive medicine would reach more people and have more permanent and far-reaching effects than if directed into medical care. We did operate six hospitals at key points to care for the more serious cases.

Many requests were made of us for assistance in developing nursing education in Brazil. We assisted in the organization and operation of four three-year nursing schools and gave consultation to several others.

Through the office of Inter-American Affairs we were able to give scholarships for study in the United States to 153 Brazilians. These scholarships were in public health, sanitary engineering, public health nursing, and the specialties

of tuberculosis, venereal disease control, child welfare, pediatrics, maternal welfare, and health education.

These people either have returned or will return to Brazil to work in the program we started or in one of the state health departments.

Will Brazil carry on this program? I think so. With the group of health workers developed and due to the fact that the program is simple and within the technical and financial means of Brazil to support, I have every reason to believe the work will continue and even be expanded. Brazil is even now putting over one million dollars a year into this special program.

I realize that in discussing these problems a rather unfavorable impression might be obtained of a wonderful country. Unfortunately the worst aspects have been presented of necessity in such a discussion, though I have attempted to tell of some of the really fine things that are being done.

I am very fond of Brazil and regard it as a great and beautiful country. The progress in almost every field that has been made in the last twenty years is astounding. There are many industrial centers developing and many new industries. Large steel mills, motor and machine factors, and textile mills are in operation. The building booms in Rio de Janeiro and São Paulo are greater than anything the United States has known, and they are showing the way in modern architecture. Great emphasis is being placed on education and schools, and cultural institutions are increasing rapidly.

In conclusion, the principal observations that were made regarding the child welfare problem in Brazil might be summarized as follows:

1. The chief causes of illness and death in adults as well as in children in Brazil are preventable diseases.

2. These diseases are due primarily to poor environmental sanitation and the lack of public knowledge regarding basic health facts.

3. The health problems are community problems and must be attacked by the health education of the leaders and the masses.

4. No child health program can be effective until a general health program is well developed.

5. Last, to show how in our special Health Organization we attempted to meet the problems by developing a simple and basic health program.

American Academy of Pediatrics

Proceedings

FOURTEENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

DETROIT, MICH., JAN. 15, 16, 17, AND 18, 1946

POST-WAR CONFERENCE ON CHILD HEALTH

Program

Tuesday

10:00 A.M. Clinics: Children's Hospital of Michigan, Herman Kiefer Hospital, Henry Ford Hospital

7:00 P.M. Child Health Activities in Brazil. Einor H. Christopherson, M.D., Assistant Director, Division of Health and Sanitation, The Institute of Inter-American Affairs

Wednesday

9:00 A.M. The Diagnosis and Treatment of Recurrent Attacks of Rheumatic Fever. Arild E. Hansen, M.D., Professor of Pediatrics, School of Medicine, University of Texas

Histoplasmosis. John H. McLeod, M.D., Washington, D. C.

Discussion. Chester W. Emmons, Ph.D., Principal Mycologist, United States Public Health Service

Facts and Figures in Pediatric Medicine. Marguerite F. Hall, M.A., Ph.D., Associate Professor of Public Health Statistics, School of Public Health, University of Michigan

12:00 N. Luncheons

The Committee on Rheumatic Fever. Alexander T. Martin, M.D., Chairman

The Committee on Coopération With Nonmedical Groups. Albert D. Kaiser, M.D., Chairman

The Committee on School Health. Harold H. Mitchell, M.D., Chairman

The Committee on Fetus and Newborn. Ethel C. Dunham, M.D., Chairman

The Committee on Mental Health. Bert I. Beverly, M.D., Chairman

2:00 P.M. Streptomycin: Clinical and Experimental Observations. H. C. Hinshaw, M.D., Ph.D., Associate Professor of Medicine, Mayo Foundation

Influenza. Thomas Francis, Jr., M.D., Professor of Epidemiology and Chairman of the Department of Epidemiology, School of Public Health, University of Michigan; Director, Commission on Influenza, Army Epidemiological Board

Report of Committee on Post-War Courses in Pediatrics. Irvine McQuarrie, M.D., Chairman

5:30 P.M. State Chairmen's Meeting

- 7:00 P.M. Poliomyelitis—Modern Treatment and Neuro-Pathology. Hart E. Van Riper, M.D., Assistant Medical Director, National Foundation for Infantile Paralysis, Chairman
- The Psychological and Psychiatric Implication of Poliomyelitis. Bronson Crothers, M.D., Clinical Professor in Pediatrics, Harvard Medical School
- The Pediatrician's Responsibility in Diagnosis and Early Care of Poliomyelitis. Philip M. Stimson, M.D., Associate Professor in Pediatrics, Cornell University Medical College; Director of the Knickerbocker Hospital, Poliomyelitis Demonstration Unit, New York City
- Neuro-Pathology of Poliomyelitis. Howard A. Howe, M.D., Poliomyelitis Research Center, The Johns Hopkins University
- Orthopedic Care of Poliomyelitis. R. Plato Schwartz, M.D., Associate Professor of Surgery, University of Rochester, School of Medicine
- The Place of Physical Medicine in Poliomyelitis. Robert L. Bennett, M.D., Director of Physical Medicine, Georgia Warm Springs Foundation, Warm Springs, Ga.

Thursday

- 8:00 A.M. Report of Committee on Post-War Planning. Warren R. Sisson, M.D., Chairman
- Report on Pending and Proposed Child Health Legislation. Joseph S. Wall, M.D., President
- The Movement in Medical Economics. Nathan Sinai, M.D., D.P.H., Professor of Public Health, Director of Bureau of Public Health Economics, The School of Public Health, University of Michigan
- 2:00 P.M. Infectious Hepatitis: Etiology and Epidemiology. Joseph Stokes, Jr., M.D., Professor of Pediatrics, University of Pennsylvania
- Acute and Chronic Infectious Hepatitis Without Jaundice. Richard B. Capps, Major, M.C., Chicago, Ill.
- Cerebral Anoxia in Pediatrics. Frederic Schreiber, M.D., Professor of Neurological Surgery, College of Medicine, Wayne University
- 7:30 P.M. Banquet

Friday

- 9:00 A.M. The Borden Award
- Business Meeting. Joseph S. Wall, M.D., Presiding
- Election of Officers
- Installation of New President

Meeting of Executive Board

Jan. 13 and 14, 1946

A meeting of the Executive Board of the American Academy of Pediatrics was held in the Book-Cadillac Hotel, Detroit, Mich., on Sunday and Monday, Jan. 13 and 14, 1946.

The first session was called to order by the President, Dr. Joseph S. Wall, on Sunday at 2:10 P.M. There were present Drs. Wall, Durand, Munns, Quillian, Stringfield, Lee Forrest Hill, Lewis Webb Hill, Pease, Bruce, Spickard, Hurtado, Martmer, and Grulee.

The first order of business was the consideration of applicants. The following applications were submitted by the Regional Committee of Region I:

Eleanor L. Adler, Yonkers, N. Y.
 Olga E. Allers, Brookline, Mass.
 Samuel R. Berenberg, New York, N. Y.

James Thomas Cameron, Quincy, Mass.
 Solkin C. Copeland, Philadelphia, Pa.
 Max D. Garber, Rochester, N. Y.
 Henry M. Glaubman, Hartford, Conn.
 Ernest F. Gordon, Yonkers, N. Y.
 Milton M. Greenberg, Washington, D. C.
 Dorothy S. Jaeger-Lee, Washington, D. C.
 Herbert B. Johnson, Kingston, N. Y.
 Edmund N. Joyner, New York, N. Y.
 Herman B. Katzman, Brooklyn, N. Y.
 William J. Kelley, Roslindale, Mass.
 Anna P. Klemmer, Lancaster, Pa.
 Lawrence Kuskin, Brooklyn, N. Y.
 Max Landsberger, Buffalo, N. Y.
 Jacob D. Leebron, Philadelphia, Pa.
 Virginia C. Lent, Hempstead, N. Y.
 Dario Morelli, Wakefield, Mass.
 Lyon M. Pearlman, Ottawa, Ont., Canada
 Louis M. Platt, Rochester, N. Y.
 Ralph Lewis Prowda, Syracuse, N. Y.
 Henry Rabnowitz, Brockton, Mass.
 Charles Kingsley Rowan-Legg, Ottawa, Ont., Canada
 William L. Rumsey, Jr., Elizabeth, N. J.
 Edward R. Schlesinger, Syracuse, N. Y.
 Samuel Silber, Brooklyn, N. Y.
 Anthony G. Stigliano, Brooklyn, N. Y.
 Edward Michael de Tona, New York, N. Y.
 Dorothy V. Whipple, Washington, D. C.

Dr. Stringfield moved that these applicants be elected to membership. The motion was seconded and carried.

The applications of Dr. Edward Michael De Tona of New York City and Dr. Jacob D. Lebron of Philadelphia were considered. It was moved by Dr. Stringfield, seconded, and carried that they be elected to membership.

The following applications were submitted by Region II:

Charles E. Anderson, Jr., Shreveport, La.
 Jay M. Arena, Duke Hospital, Durham, N. C.
 John M. Lee, Nashville, Tenn.
 Thistle M. McKee, Alexandria, Va.
 Martin G. Neely, Birmingham, Ala.
 Benjamin Owen Ravenel, Charleston, S. C.
 George W. Salmon, Houston, Texas
 John Hostley Soady, Asheboro, N. C.
 Jack Tepper, Chattanooga, Tenn.

It was moved by Dr. Bruce, seconded, and carried that these applicants be accepted. The following applications were submitted from Region III:

Mary Daniel Ames, Detroit, Mich.
 George E. Anthony, Flint, Mich.
 Philip L. Aries, Chicago, Ill.
 Katherine Howard Baird, Wauwatosa, Wis.
 Rowine Hayes Brown, Chicago, Ill.
 Robert Peers Buckley, Duluth, Minn.
 Frank Stephen Cross, Lansing, Mich.
 Eugene Gettelman, Chicago, Ill.

Sidney A. Kauffman, Indianapolis, Ind.
 Willard Z. Kerman, Chicago, Ill.
 Ernest Robbins Kimball, Jr., Evanston, Ill.
 Herbert C. Miller, Kansas City, Kan.
 Howard R. Miller, Peoria, Ill.
 Wesley Stephan Nock, Chicago, Ill.
 Glenn B. Patrick, Elkhart, Ind.
 Iwan Rosenstern, Evanston, Ill.
 Ashley Weech, Cincinnati, Ohio

It was moved by Dr. Lee Forrest Hill, seconded, and carried that these applicants be accepted.

The following applications were submitted from Region IV:

Ellis W. Adams, Great Falls, Mont.
 William Thomas Auld, Stockton, Calif.
 Donald J. Bourg, Portland, Ore.
 Mollie Chalfin, Oakland, Calif.
 Carl A. Erickson, Pasadena, Calif.
 John Richard Jimerson, Long Beach, Calif.
 Harry R. Lusignan, Monterey, Calif.
 Roderick A. Norton, Tacoma, Wash.
 Gordon L. Richardson, Hollywood, Calif.
 Harold Weatherman, San Diego, Calif.

It was moved by Dr. Spickard, seconded, and carried that these applicants be accepted.
 The following applications were submitted by Region V:

Waldyr de Abreu, Rio de Janeiro, Brazil
 Humberto Arroyo Parejo, Caracas, Venezuela
 Alvaro Serra de Castro, Rio de Janeiro, Brazil

Dr. Hurtado moved that these applicants be accepted. The motion was seconded and carried.

The following were elected to Emeritus Fellowship:

William N. Bradley, Philadelphia, Pa.
 Guy I. Bliss, Long Beach, Calif.
 Howard C. Carpenter, Philadelphia, Pa.
 James Dunn, Davenport, Iowa

The following resignations were accepted:

Herbert Archibald, Oakland, Calif.
 Charles N. Sturtevant, Philadelphia, Pa.
 Henry P. Wright, Montreal, Que., Canada

Dr. Franklin Henry Top, Detroit, Mich., was elected to Associate Membership.

Dr. Grulee reported that the name of Dr. Donald Patterson of London, England, had been suggested for Honorary Fellowship. It was moved, seconded, and carried that Dr. Patterson be elected to Honorary Fellowship.

The names of three men in arrears for dues were presented and the Secretary was instructed to notify them that unless dues were paid to date they would be dropped from membership.

The report of the President was presented by Dr. Wall.

The report of the Secretary was presented by Dr. Grulee. It was moved, seconded, and carried that the report be accepted.

The report of the Treasurer was presented by Dr. Grulee. The salaries of the office assistants were discussed by Dr. Grulee. It was moved, seconded, and carried that Mrs. Bundy's salary be raised to \$250 a month and that of Mrs. Fuger to \$150 a month (she is paid an additional \$25 for assistance to Dr. Grulee in editorial work).

In the absence of Dr. Grulee and Dr. Martmer, their salaries were discussed by Dr. Wall. It was moved, seconded, and carried that Dr. Grulee's salary be increased to \$12,000 a year and Dr. Martmer's to \$2,000 a year. All salary increases to take place as of January 1.

The next order of business was the report of the Regions.

The report of Region I was accepted as published. It was moved, seconded, and carried that the name of Dr. Paul W. Beaver of Richester, N. Y., be recommended to the President for appointment as Associate Regional Chairman of Region I.

The report of Region II was accepted as published.

The report of Region III was accepted as published. It was moved, seconded, and carried that the name of Dr. Roger Kennedy of Rochester, Minn., be recommended to the President as Associate Chairman for Region III.

The report of Region IV was accepted as published.

The report of Region V was discussed by Dr. Hurtado. It was moved by Dr. Hurtado, seconded, and carried that the President appoint a committee consisting of members of the Executive Committee and of the Latin-American group to consider the subject of a Pan-American Congress in 1948, the committee to report at the annual meeting in 1946.

The question of dues for Region V was discussed by Dr. Hurtado. It was moved by Dr. Hurtado, seconded, and carried that as the result of his knowledge of the situation the dues for members in Cuba, Brazil, Colombia, and the Dominican Republic be made the same as the dues of members in the United States, namely, \$20 a year, and that the dues for members in the remaining countries be made \$10 a year except for new members elected after July 1, 1946, who would pay \$20 a year.

The meeting recessed for dinner at 5:40 P.M. and reconvened at 8:00 P.M.

The first order of business was the reports of Standing Committees with State Activities.

The Secretary read a letter from Dr. Fairfax Hall concerning the work of the Committee on Contact Infections and in which he tendered his resignation as Chairman of the Committee. It was moved, seconded, and carried that the resignation of Dr. Hall be accepted and that the incoming President appoint his successor as Chairman and another member of the Committee.

The report of the Committee on Cooperation with Nonmedical Groups was accepted as published.

The report of the Committee on Governmental and Medical Agencies was accepted as published.

The next order of business was the report of Standing Committees.

The report of the Committee on Fetus and Newborn contained questions by Dr. D. Lesesne Smith concerning the use of penicillin in place of silver nitrate for eye prophylaxis, and by Dr. Jerome Glaser concerning the definition of the newborn period. It was moved, seconded, and carried that the Secretary write the Chairman of the Committee instructing the Committee to continue its investigations concerning the use of penicillin in place of silver nitrate and report at a future meeting.

Concerning the letter of Dr. Glaser, it was moved, seconded, and carried that the Executive Board concur in the recommendation of the Committee.

Dr. Wall presented the report of the Committee on Legislation.

Dr. Grulee reported for the Committee on Pan-American Scholarships.

Dr. Grulee reported for the Committee on Pediatric Awards.

Dr. Martmer reported for the Program Committee.

The next order of business was the reports of Special Committees.

Dr. Martmer reported regarding redistricting the Academy. It was moved by Dr. Stringfield, seconded, and carried that the report of the Committee on redistricting the Academy be accepted, that the report be mimeographed and copies presented to the members at this meeting; that the question be voted on at the next annual meeting of the Academy

along with such changes in the by-laws as would make them consistent with the new districting of the Academy.

Dr. Martner reported concerning life membership in the Academy. It was moved by Dr. Munns, seconded, and carried that the report be held over for consideration for one year. It was moved by Dr. Stringfield, seconded, and carried that the Committee be thanked by the Executive Board for their report.

The meeting adjourned at 9:55 P.M.

The Monday morning session was called to order by the President at 10 A.M. In addition to the members of the Executive Board there were present by invitation Drs. Hugh McCulloch, Warren Sisson, and John Hubbard.

The first order of business was the report of the Committee on Cooperation with the American Legion by Dr. McCulloch. It was moved, seconded, and carried that the report be accepted.

The next order of business was the report of the Committee on Rheumatic Fever by Dr. McCulloch. It was moved, seconded, and carried that the recommendations of Dr. McCulloch that the Executive Board approve the Council on Rheumatic Fever as established under the articles he presented and appropriate the sum of \$100 for membership in the Council.

Under unfinished business, the Secretary stated that Dr. Hurtado had proposed the name of a Havana pediatrician for Honorary Membership. It was moved, seconded, and carried that the former action of the Board be applied in this case, namely, that no honorary members are elected from the United States, Canada, or Latin America.

The report of the Committee on Geographical Distribution of Pediatricians was received. It was moved, seconded, and carried that the report be accepted and the Secretary was instructed to write a letter of commendation to Dr. Goehle.

The Secretary read a letter from Dr. Carl H. Smith requesting that the Committee on National Defense be continued, and it was so ordered.

Dr. Grulee reported for the Committee on Post-War Courses in Pediatrics.

The report of the Committee on Post-War Planning was presented by Dr. Warren Sisson who, in turn, introduced the Executive Secretary, Dr. John Hubbard. Dr. Hubbard outlined the proposed plan.

It was moved, seconded, and carried that the Executive Board confirm the appointment of Dr. Hubbard at a salary of \$10,000 a year.

The question of obtaining funds for the work of the Committee was discussed. It was moved, seconded, and carried that this matter be tabled until a subsequent meeting of the Board to give Dr. Grulee opportunity to make some investigation.

The report of the Committee on Tumor Registry was accepted.

The Nominating Committee presented the following report:

President-Elect: Dr. Lee Forrest Hill
Chairman of Region III: Dr. George F. Munns

The meeting recessed for luncheon at 1 P.M. and reconvened at 2 P.M.

Dr. Martha Eliot was present by invitation.

The first order of business was the report of the American Board of Pediatrics by Dr. Lee Forrest Hill. It was moved, seconded, and carried that the report be accepted.

Dr. Martha Eliot discussed the relations of the Academy with the Children's Bureau and answered questions put to her by the members of the Board.

The Committee then took up miscellaneous business. The Secretary read a letter from Mr. Stein regarding framing of certificates.

The Secretary read a letter from the American Public Relations Association concerning annual Public Relations Awards.

The Secretary read a letter concerning the National Planning Association. Dr. Stringfield said he had been directed by the President to attend a meeting of this organization in New York. It was moved, seconded, and carried that Dr. Stringfield be continued as an observer of this organization.

The Secretary read a letter from Dr. Henry G. Poncher regarding scientific exhibits. It was moved, seconded, and carried that the Secretary handle this matter and report at the June meeting of the Executive Board.

Dr. Wall said he had received a letter from Dr. Harold Mitchell concerning the National Council of Scientific, Professional, Art, and White Collar Organizations. It was agreed that Dr. Mitchell should continue as an observer of this organization.

The Secretary read a letter from Mr. A. L. Rose pertaining to the translation of the Child Health Record into Spanish. The request was granted.

The Secretary read a letter from Dr. John A. V. Davies in referring to special events connected with the meeting of the Academy and his disapproval of same.

The Secretary read a letter from Dr. Harvey F. Garrison concerning hotel reservations. It was moved, seconded, and carried that the Secretary be authorized to reply to Dr. Garrison that he is not responsible for the reservations of State Chairmen.

The Secretary read a letter from Dr. Leona Baumgartner regarding French pediatricians.

The proposed changes in the By-Laws supported by the Executive Board at its meeting June 15, 1945, had been sent to the membership by mail and the vote was 172 for acceptance and 1 against. It was moved, seconded, and carried that the vote of the membership be approved for the following changes:

Article III, Section 2, page 11, the words *with the exception of Region V* be deleted.

Article III, Section 4, page 11, following the word "President," *annually* be inserted followed by a *comma*.

In the same section, page 12, top line, a *comma* be inserted after "Regional Chairmen."

The Secretary read a letter from Dr. Coe asking that a section on Surgical Diseases of Children be included in the Academy program. It was moved, seconded, and carried that the Secretary write Dr. Coe and tell him that at the next meeting a round table on the subject will be provided.

The Secretary requested that he be empowered by the Executive Committee to resign from the Advisory Committee of the Children's Bureau. It was suggested that the matter be held over until the next meeting.

The question of publicity was discussed by the Secretary. He was instructed to discuss with Mr. Selz the cost of a permanent publicity man.

The question of holding an International Congress on Pediatrics was presented by Dr. Helmholtz. It was moved by Dr. Spickard, seconded, and carried that it be the consensus of opinion that in view of the proposed Pan-American Congress in 1948, that the question of holding an International Congress be deferred until after the meeting of the Pan-American Congress.

The question of the place and time of the next annual meeting was discussed. It was moved, seconded, and carried that the time and place be left to the President and Secretary, with the preference for the Southwest, particularly Dallas.

The President said that last year the Board authorized the expenditure of \$25 for membership in the Child Welfare Information Service. It was moved, seconded, and carried that \$25 be again subscribed.

The meeting adjourned at 6 P.M. to meet on Tuesday at 5 P.M. and again on Thursday, at 12 o'clock noon.

Report of Committee on Redistricting Membership

Report of the committee appointed by the president on the recommendation of the Executive Board of the American Academy of Pediatrics to consider the redistricting of the membership on the basis of number of members so as to provide for more equitable representation on the Executive Board.

The committee submits the following plan:

HISTORICAL

At the time the Academy was organized it was necessary to provide some form of equitable distribution of the representation on the Executive Board. With this in mind the four regions with which we are all familiar were set up. A natural division was into the Eastern, Southern, Middle Western, and Far Western States.

With the passage of time it has become evident that such a division has ceased to be a satisfactory method of providing representation on the Executive Board. With the large increase in membership of the Academy it has been suggested that the problem of redistricting be studied so as to provide equitable representation on the basis of number of members.

This committee proposes that the United States, Canada, Hawaii, and Puerto Rico be divided into eight (8) districts of approximately equal numbers of members. District 9 would comprise the Latin-American countries now constituting Region V.

Each district would be represented on the Executive Board by a district chairman who would represent the members of his district as well as serve in the same capacity as the present Regional Chairman.

District Chairmen would be elected by the membership in the same manner as is now provided for the election of Regional Chairmen and would serve for a period of eight (8) years. In this way there would be one new member of the Executive Board elected each year so as to provide stability to the Executive Board and at the same time assure a constantly changing membership.

Under such a plan the present regional activities which consist almost entirely of the arranging of Clinical Meetings in the spring of each year would be discontinued and in place of such Regional Meetings it is proposed that a spring meeting or meetings would be provided through the effort of the Academy and the Secretary's Office. Such meeting or meetings would be held at strategic cities throughout the United States so as to afford those members who were not able to attend the Annual Meeting in the fall an opportunity to attend a Clinical Meeting at which subjects could be presented which should be brought to the attention of the membership.

In this connection the meeting of the Executive Board in the spring could coincide with one of these meetings and enable the membership and the Executive Board to discuss matters of mutual interest.

Under such an arrangement the regional groups would be relieved of the responsibility for arranging such meetings as well as the financial responsibility which has proved a burden in some instances.

Such a meeting or meetings could be expected to pay their own way through the sale of exhibit space because of the greater attendance which would be assured through making them open to all members of the Academy as well as to others interested in pediatrics if the Executive Board should feel this would be a proper course.

Should the Executive Board feel that one meeting a year is sufficient it would still be possible under such an arrangement as has been suggested for the State Chairmen of the various districts to get together at such times as might seem advisable.

RECOMMENDATIONS

1. That the Executive Board submit to the membership the proposal that the Academy redistrict Regions I, II, III, and IV into eight (8) districts based upon an equal number of members in each district.
2. That the districts be represented by a district or Regional Chairman with all the duties and responsibility now held by a Regional Chairman.
3. That nominations and election of such Regional Chairmen be done in the manner now prescribed in the Constitution.
4. That the term of office of a District Chairman be for a period of eight (8) years.
5. That the Executive Board be empowered to make all necessary changes in the Bylaws of the American Academy of Pediatrics to accomplish the Redistricting as proposed in this report.

<i>District 1</i>		<i>District 7</i>	
Maine	6	Kansas	8
New Hampshire	5	Missouri	42
Vermont	6	Oklahoma	14
Massachusetts	78	Arkansas	4
Connecticut	60	Texas	78
Rhode Island	14	Louisiana	27
Quebec	19	Tennessee	31
Total	188	Mississippi	11
		Alabama	21
		Total	236
<i>District 2</i>		<i>District 8</i>	
New York	210	Montana	4
<i>District 3</i>		Idaho	3
Pennsylvania	118	Wyoming	1
New Jersey	74	Utah	8
Delaware	6	Nevada	2
Total	198	Colorado	17
<i>District 4</i>		Arizona	7
Maryland	27	New Mexico	4
Washington, D. C.	33	British Columbia	3
W. Virginia	9	Washington	20
Virginia	31	Oregon	9
N. Carolina	24	California	131
S. Carolina	11	Hawaii	3
Georgia	33	Total	212
Florida	27		
Puerto Rico	3		
Total	198		
<i>District 5</i>		<i>District 9</i>	
Michigan	80	The Latin-American Countries	158
Indiana	20		
Ohio	92		
Kentucky	16		
Ontario	18		
Total	226		
<i>District 6</i>			
North Dakota	3	District 1	188
South Dakota	2	District 2	210
Nebraska	13	District 3	198
Minnesota	33	District 4	198
Iowa	15	District 5	226
Wisconsin	19	District 6	221
Illinois	134	District 7	236
Saskatchewan	1	District 8	212
Manitoba	1	District 9	158
Total	221		

Report of Committee on Post-War Planning

Thursday, January 17

PROGRESS AND PLANS OF THE STUDY OF CHILD HEALTH SERVICES

DR. WARREN R. SISSON, CHAIRMAN OF COMMITTEE, AND
DR. JOHN P. HUBBARD, DIRECTOR OF STUDY

AT THE meeting of the American Academy of Pediatrics in Detroit, Jan. 14-18, 1946, there was much discussion of the progress and plans of the Study of Child Health Services in meetings of the Executive Board and State Chairmen, as well as more detailed consideration by the Committee for the Study of Child Health Services. Furthermore, a panel

discussion was presented to a general meeting of the Academy on the morning of Jan. 17, 1946. Rather than reporting the minutes of these meetings in full, they are summarized here.

MEETINGS WITH THE EXECUTIVE BOARD

In meetings held with the Executive Board, Drs. Sisson and Hubbard reviewed the development of the Study since its adoption by the Academy at the annual meeting in St. Louis in November, 1944.

Careful consideration was given to the proposed budget. It was realized soon after the Study was first undertaken that the original \$8,000 was going to turn out to be a relatively small item to prime the pump. The budget which has now been drawn up to show the total cost of the Study for a period of two years from the present date, includes:

1. \$29,000 apportioned to the Academy to cover salaries of the Director, Assistants, and their travel
2. \$69,400 apportioned to the United States Public Health Service, representing the salaries of personnel assigned to the Study and the value of coding and statistical equipment supplied by the Public Health Service
3. \$25,900 apportioned to the Children's Bureau representing the salaries of personnel assigned to the Study by the Children's Bureau
4. \$111,800 which it is anticipated should be made up by the States in order to finance in part the cost of the Study within their own boundaries
5. \$203,800 from other sources for the costs not covered above of salaries and travel of additional personnel, office expenses, printing, etc.

The total budget made up on this basis is \$439,900. As reported elsewhere in the minutes of the Executive Board, action was taken to approve this budget and to appoint a Ways and Means Committee to attempt to raise the amount of approximately \$200,000 apportioned to "other sources." Furthermore, it was voted to withdraw from the reserve fund of the Academy an additional \$10,000 for the expenses of the Study.

Attention is also directed to the fact that the Executive Board voted to change the name of the committee of nine, of which Dr. Sisson is Chairman, from the Committee on Post-War Planning to the Committee for the Study of Child Health Services.

SUMMARY OF DISCUSSION AT GENERAL MEETING AND AT MEETING WITH STATE CHAIRMEN

Panel Discussion Presented to General Meeting.—A panel discussion was presented to a general meeting of the Academy on the morning of Jan. 17, 1946, as follows:

1. General Scope and Purpose, Dr. Warren R. Sisson, Chairman
2. Administrative Organization, Dr. Charles L. Williams, Jr., Executive Secretary from the United States Public Health Service
3. Questionnaire Schedules, Dr. Katherine Bain, Executive Secretary from the Children's Bureau
4. Review of the Pilot Study in North Carolina, Dr. Arthur H. London, Jr., State Chairman from North Carolina
5. Further Conduct of the Study, Dr. John P. Hubbard, Director of Study
6. What Do We Hope to Get Out of It? Dr. Henry F. Helmholz

In discussing the scope and purpose of the Study, Dr. Sisson emphasized the importance of keeping in mind the original objective and quoted from the resolution adopted by the Academy in St. Louis in 1944: "To make available to all mothers and children in the U. S. A. all essential preventive, diagnostic, and curative medical services of high quality, which used in cooperation with the other services for children, will make this country

an ideal place for children to grow into responsible citizens." And as a first step toward this end, the recommendation "that the American Academy of Pediatrics request the United States Public Health Service and the Children's Bureau to undertake with the Academy a survey in every state to determine . . . information concerning the present situation and extension of personnel and facilities needed in each state to meet the objectives as stated. . . ."

The content of the Study falls into four major fields of inquiry: pediatric education; distribution, qualification, and activities of professional personnel; hospital and clinic facilities; and general health services.

1. *Pediatric Education.*—Basic to any study concerned with health of children is a study of education of physicians in pediatrics, both general practitioners and specialists. It is proposed to make a study of the sixty-six medical schools in the country to determine the quantity and quality of training in pediatrics: undergraduate, intern and resident, postgraduate for general practitioners, pediatric nursing, and others. Data will be obtained on staff, curricula, number of pediatric beds available for teaching, and opportunity for study of pediatric specialties such as allergy, rheumatic fever, and mental hygiene.

This part of the study will be carried out on a national basis, rather than State by State, and will be the responsibility of a special committee composed of pediatricians well qualified in the field of medical education.

2. *Distribution, Qualifications, and Activities of Professional Personnel.*—It has long been recognized that most of the pediatricians are in cities, but that even there much of the care of children is given by general practitioners. In this part of the study, data will be collected on distribution of pediatricians (diplomates and nondiplomates), general practitioners and specialists competent to handle certain specialized care of children, as surgeons, allergists, cardiologists, and psychiatrists. Information will be sought in each community concerning availability of physicians and facilities for procedures essential for emergency diagnosis and therapy of sick infants such as: transfusing newborn infants including Rh typing, provision of intravenous fluids, provision of artificial respiration and oxygen, facilities for tracheotomy, and essential bacteriological and chemical determinations. An attempt will be made through special questionnaires to estimate the amount of time devoted by general practitioners to the care of children, and the extent to which they have had postgraduate training in pediatrics. It is hoped also to gather data from pediatricians relating to size of case load, through recording of cases seen in a definite period, as for one week or one month, in the home, office, hospital, or in consultation.

3. *Hospital Facilities, Including Outpatient Clinics, and Laboratories.*—Fortunately, a comprehensive study of hospitals by the Commission on Hospital Care is already under way. Much of the material being gathered in the hospital survey is identical with that desired by the Academy survey, though much more detailed material on pediatric and newborn care is needed. Arrangements are being made to use material from the hospital survey and to supplement this with data obtained on a supplementary schedule. Data on outpatient clinics and on laboratories are to be included.

4. *Health Services for Children.*—The survey will cover the extent and quality of such services as child health conferences, school health services, medical care programs, immunization services, child guidance services, and public health nursing. Some of the information can be supplied by State health agencies. Other parts will have to be gathered directly.

The administration of the Study has been organized under the guidance of the Committee made up of nine, all of whom are members of the Academy. An additional Advisory Committee consists of Dr. Joseph S. Wall, Dr. Martha M. Eliot, and Mr. George St. J. Perrott. The central executive and administrative committee is as follows: Dr. John P. Hubbard, Director, Drs. Katherine Bain and Charles L. Williams, Jr., Executive Secretaries.

The central office has been established in Washington. It is, in a way, considered unfortunate that the center of the Study is in Washington, D. C., suggesting to some that this is therefore a Federal project. It is very definitely not a Federal project, but rather an undertaking of the Academy with the primary responsibility remaining in the hands of

the Academy. Only by virtue of the generous and essential assistance of the two cooperating government agencies has it seemed wise in promoting the efficient conduct of the Study to have the office in Washington where full advantage may be taken of the personnel and resources of their statistical divisions. In addition to the executive staff, a limited field staff will be added to assist States to organize the study locally and to carry out that portion of the study dealing with pediatric education. This field staff, together with members of the executive staff, will contact State Pediatric Organizations, stimulate their interest in the survey and render consultative service to the State executive staffs. After the first year of the study, the field staff will serve to maintain contact with local groups, leaving the central executive staff relatively free to analyze and study the data collected and to prepare a report.

It is felt that the part of the survey dealing with pediatric education, which largely concerns medical schools, can best be made by a staff working out of the central office. Where possible, however, local interest and participation will be invited.

In each State it is proposed that the State Chairman of the Academy appoint a study committee of Academy members with himself, or someone appointed by him, to act as chairman. In addition there should be a State advisory committee composed of representatives from such groups as State Board of Health, hospital association, nursing organizations, welfare groups, farm groups, labor, and others. Subcommittees of technical members could be formed as needed, or individual members could be called on for technical advice.

The State Staff to work under the Academy committee should consist of at least one full-time medical or nonmedical person to act as executive secretary and one clerk-stenographer. Large States may need two or three people, while small States can operate with one, or even possibly part-time services.

North Carolina was chosen for a pilot study in order to test methods and establish procedures before undertaking the study throughout the rest of the country. The Study was supervised by the State Chairman of the Academy; the executive secretary was a health officer on loan from the United States Public Health Service. Enthusiastic support was given by the State Health Department, pediatricians, general practitioners, dentists, and lay groups. Much valuable experience was gained from the use of the survey schedules which were developed to obtain the necessary information on the State level. These schedules are divided into three series. The first series had been integrated with those already being filled out by the Hospital Commission and will serve to supplement them with data of pediatric interest. The second series deals with general health services such as preventive services available in health jurisdictions, medical well-child conferences, dental services, mental hygiene services, services for the physically handicapped, communicable disease control, school health and public health nursing. The third series is intended to obtain information from personnel engaged in private practice: pediatricians, general practitioners and dentists. With the Study in North Carolina now reaching a successful conclusion, it is ready to be launched in other States.

The results to date from North Carolina have been very gratifying. The groundwork and plan of attack were formulated about the middle of October, 1945, and by Jan. 1, 1946, every schedule had been mailed out and a good percentage of them was being returned. The thirty-seven pediatricians of the State were the central focus of the Study; the cooperation received from them was the keynote of its success. To as large an extent as possible, their load was lightened by the efforts of the executive secretary. Letters were prepared for their signature to be sent to the general practitioners, hospitals, and health agencies with whom they were requested to get in contact. Of the total number of general physicians and surgeons (2,034) throughout the State, 60 per cent have returned their questionnaires up to date. In comparison with the normal expectancy of returns from questionnaires of this nature (about 33 per cent) this is a very gratifying result. The questionnaires dealing with general health services were handled with the cooperation of the Public Health Department of the State. Of the total of seventy-two sent out to the Health Districts, returns have been received from fifty-eight, or 81 per cent, and it is expected that a complete 100 per cent result will be obtained soon.

In a detailed description of the questionnaire schedules, Dr. Bain emphasized the fact that they are not yet considered in final form. They have been through many revisions, and they are to be revised again in the light of the experience gained in North Carolina. Revised schedules, instructions for their use, and suggestions resulting from the Pilot Study are now being put together in the form of a field manual for the use of State Chairmen and Executive Secretaries.

In describing the further conduct of the Study, Dr. Hubbard emphasized the responsibility of the pediatricians themselves. The Study was originally undertaken as a result of action arising in a meeting of the Academy as a whole. It is an attempt on the part of physicians to evaluate health services rendered by themselves and others concerned in the health and welfare of children. This effort will be successful only in so far as the responsibility is felt and accepted by each and every individual member of the Academy. In order that the Study may get well under way before this coming summer, the State Chairmen were requested to give thought now to the organization of programs within their own States so that they may be prepared to launch the Study in their respective areas by the first of March. This then would allow from three to four months for the actual conduct of the Study before the summer season. If it does not get well under way before summer, it will drag into next fall and winter and much of its purpose and value will have been lost.

Much discussion revolved around the question of the use to which the material gathered from the States is to be used. One of the valuable aspects of conducting the study of health services at the State level is that each State can work out its own pattern in accordance with local conditions. Having done so, each State will then have factual material available which may serve as a basis for drawing up plans for improving the health services within its own boundaries. Some States may choose to analyze the data themselves in their own way for their own purposes. There can be no objection to such a procedure. To all States will be made available the results of the Study following the digestion and analysis by the central technical staff. Eventually, and it is to be hoped that it will be without delay, a factual report will be published. Certain of the State Chairmen questioned the use to which this report will be put. It is not considered the function of the Study personnel to determine at the present time how this material is to be used. Obviously the whole Study will be valueless unless it can serve as a basis for recommendations to be made at a later date on the foundation of solid factual data. But the Study personnel is not concerned with the formation of recommendations; the job in hand is to gather the facts and analyze them as accurately and honestly as possible for presentation to the Academy. It will then be the responsibility of the Academy or its chosen representatives to outline any course to be taken as a result of the Study. Assurance was given by the Director that we are not now concerned with steering the ship in any particular direction but rather in determining what equipment it has aboard.

DISCUSSION

DR. HENRY F. HELMHOLZ.—We hope to get from this study information which will enable us to outline measures for insuring proper care of infants and children in every state in the union as well as in the various parts of the States. You have heard how the Study Committee of the Academy with the splendid help and cooperation of the Children's Bureau and the Public Health Service is attacking the problem and how it hopes eventually to gather the necessary information that will make it possible to outline for each community of each state the necessary steps to serve the local child population adequately. It will give us for the first time, on a national scale, the scope of the problem and the great variations in the type of medical care available at present and what type of care is necessary to develop for children in different parts of the country.

It has already been shown that a medical organization, the American Academy of Pediatrics, can set up an investigation for the welfare of American children so well that it meets the approval of two governmental agencies and they are willing to back the investigation with means that far exceed ours. By the cooperation of the Academy, the Children's Bureau, and the Public Health Service, the present status and essential needs for children in

all parts of our country can be determined. This information is fundamental before any adequate program of infant and child care can be worked out. It should bring out as never before where the pediatrician fits into a child care program for all children.

What are the functions of a pediatrician? Are we pediatricians fulfilling our entire duties when we all continue to do general practice limited to an age period? There are only enough pediatricians to care for one-tenth of the children on this basis. How are we going to influence the life of the other nine-tenths of the child population that do not have access to the care of a pediatrician? Do we plan to increase our number tenfold to care for all the children or shall we function by raising the standard of child care given by the general practitioner? As educators in a graduate school system or as consultants in state and county health departments?

Unless we have definite ideas as to the solutions of these problems, we will not be in a position to offer constructive advice to the national planners of child health. As you know, there are several bills before Congress now that have to do with child health, all with the object of giving greatly increased services to children. It is my belief that our survey or a similar survey must be available before the work can be started. It would seem that state plans, and the planning is to be on a state basis, cannot be made without such a survey. It would require many months of work by the state departments of health to gather the information that the Committee aims to obtain in its study. Since the training of the necessary personnel will take many additional months, I am not worried that legislation will be passed before the Committee completes its study.

At this point it is well to recall that in 1910 there was not a well-organized clinic in the United States for the training of pediatricians, there was no pediatric research as such, and today, according to the opinion of foreigners, this country leads the world in this field. This is an accomplishment in education and research of which all may well be proud. Pediatric education has by no means reached its limits and there is still great need for pediatric research. It is this function of still further raising standards that deserves closest attention. I am hopeful that our survey will indicate the way in which this can be accomplished most successfully and economically. If the care of all children in this country is to be of the highest order, will it be necessary to develop a new type of pediatrician, one who acts only as a consultant as the English type of pediatrician does or will this new type be an educator, as well as consultant? Will pediatric allergists, cardiologists, gastroenterologists, urologists, and all the rest have to develop, or will the development of hospital units which are small at the periphery and complete centrally, adequately solve the problem of the unusual diagnostic cases?

I think our survey is going to be helpful in demonstrating the stupendous size of our problem and the necessary strides we will have to make if we are to measure up to the needs that this survey will show. There is much work for the pediatrician to do. There is need for many more highly trained pediatricians if all the children in this country are to be adequately taken care of.

Just as the pediatricians in the past have led the way in the application of preventive measures to medicine, so the survey which our Committee is making should indicate to the medical profession how the entire problem of medical care for all, both preventive and curative, is to be attacked and plans made for its solution.

THE CHAIR.—If we had not had in Washington a man of Dr. Wall's peculiar ability to represent the Academy, I do not believe in the Academy membership we could find a man as able to do the work he has done or a man who would give more time and sincere thought to it than Dr. Wall. Dr. Joseph S. Wall, who has promised to stay on the job when he is no longer president, will now give the report of the Legislative Committee.

Report of Pending and Proposed Legislation on Child Health

This report on legislative proposals must be made in a dual role, the recorder holding two portfolios in the cabinet of the Academy, to wit, that of president and of chairman of

the committee on legislation, having been continued in the latter post during the past year by direction of the Executive Board.

A considered effort will be made to present to the Fellows of the Academy a factual and documentary report of the creation and content of proposed congressional bills affecting their interests and those of the specialty to which we are devoted.

An analysis of legislation must of necessity point out features which in the opinion of your officials appear inimical to our profession of pediatrics and to medicine in general, of which we are necessarily a part. But it must be borne in mind that such a story to a certain extent reflects the personal views of the historian and that in its recital the listener should heed the caution of radio that the views expressed by the commentator are his own and not necessarily those of his sponsor, the Academy of Pediatrics.

The very purpose of this session today is to bring to light the opinions of our members through free discussion of the problems which now confront us so as to crystallize the Academy's beliefs as a committee of the whole in general meeting.

There are now before the Congress three measures in which we possess an intimate interest as all three purpose the extension of health services to mothers and children so that far greater accomplishment for their health and welfare may be achieved in the future, which represents the very goals for which this Academy was founded and toward which it has constantly labored since its inception.

The Academy's record in the past, from an altruistic and humanitarian standpoint, cannot be challenged and its continued activity in such direction with even increased momentum will be related to you this morning by Dr. Sisson, chairman of the postwar study group constituted by you at the St. Louis meeting of last year.

The aims of the Academy and of its individual members are encompassed in the first paragraph of this committee's original report, namely: "To make available to all mothers and children in the United States of America all essential preventive, diagnostic and curative medical services of high quality, which used in cooperation with the other services for children, will make this country an ideal place for children to grow into responsible citizens."

Our objectives and aspirations coincide exactly with those of the more vocal social and political reformers, utopian evangelists, and some fanatical crusaders whose enthusiasm too often outruns the boundaries of common sense and realism. We, too, seek diligently the Holy Grail, symbolic of perfection in mother and child protection from the vicissitudes of ill health. Our quest differs not from that of the social crusaders, our goals and desires are equally alike, but the methods of attaining these ends, from our point of view, do not agree in many respects with the programs thrust upon us, usually without our knowledge and without the utilization of that experience we possess in the practice of pediatrics which should be recognized as necessary in determining the success or failure of any projected planning for child betterment.

S. 191, the so-called Hill-Burton bill, has now passed the Senate and has been sent to the House. The bill was entirely rewritten in committee before its adoption by the upper house of Congress to which it was presented under the title, "Hospital Survey and Construction Act."

S. 191 proposes a program of Federal grants-in-aid to assist the States:

1. To determine their hospital and public health facility needs through state-wide surveys

2. To develop state-wide programs for construction of facilities needed to supplement existing facilities so as to furnish adequate hospital, clinic, and other similar services to all the people of the State

3. To construct such facilities for public and voluntary nonprofit hospitals and for public health centers in accordance with such programs

The kinds of facilities which could be constructed under the program:

1. Public health centers—which are defined to mean a publicly owned facility for the provision of public health services, the scope of which would be a matter for determination by State law

2. Hospitals—general, tuberculosis, mental, chronic disease, and other types except those furnishing primarily domiciliary care

3. Related facilities such as laboratories, outpatient departments, nurses' homes, and training facilities, and central service facilities operated in connection with hospitals

As used in this bill, the term "construction" is also broadly defined to include:

1. Construction of new buildings

2. Expansion, remodeling, and alteration of existing buildings

3. Initial equipment of such buildings

4. Landscaping the site, architects' fees, legal counsel, and all other expenses incidental to construction, excluding the cost of off-site improvements, and, except in case of public health centers, the cost of acquisition of land.

The bill is one requiring "matching," the range of Federal percentages allotted would vary from 75 per cent for the poorest States to 33½ per cent for the wealthiest States.

The administration of the Hill-Burton Hospital Survey and Construction Act is vested in the Surgeon-General of the United States Public Health Service with certain powers assigned to the Federal Security Administrator, who appoints a Federal Hospital Council to consist of nine members and who is given the right of approval or disapproval of administrative regulations made by the Surgeon General. Should the Surgeon General refuse to approve any application for hospital construction, or should the State be dissatisfied with the action of the Surgeon General, "such State may appeal to the U. S. Circuit Court of Appeals for the circuit in which such State is located," with the right of further appeal or review by the U. S. Supreme Court.

The original Hill-Burton hospital construction bill met with the approval of the American Medical Association and of the various hospital organizations.

On November 19, 1945, the President transmitted to the Congress a message containing a request for legislation for adoption of a national health program. (Seventy-ninth Congress, first session, document 380.)

Upon the same day, immediately following the reading of the President's message, Messrs Wagner, Murray, and Dingell deposited in the legislative hoppers their fourth National Health Act, now numbered S. 1606, the last three figures being reminiscent of one of many great accomplishments of medical therapeutics in recent years, achieved under a system of free enterprise.

This latest legislative proposal emanating from the triumvirate of Shadrach, Meshach, and Abednego, reappeared on the scene from their fiery furnace where medicosocial legislation is welded, contains many new, supposed concessions to practitioners of medicine, evidently inserted in an effort to remove opposition, such as: the right of choice of physicians, which right is in reality subject to marked limitations, the choice of methods of payment of medical fees and other blandishments of supposed allure.

S. 1606 in Title I, Part A, is concerned with grants to States for Public Health Services, more especially the control of venereal disease and of tuberculosis but states that the term "public health work" shall include customary and accepted functions, services, and activities of public health agencies, all of which are enumerated in some detail.

At the close of this section [Part A (1)] there occurs a remarkable pronouncement in view of the accepted conception of public health measures, to wit: "The term does not include: construction of hospitals, water supplies, sewerage or other waste-disposal systems, or of other facilities; operation or maintenance of hospitals (except hospitals for persons afflicted with infectious diseases), water supplies, sewerage or other waste-disposal systems; and related matters." Such hygienic considerations certainly enter into the question of mortality and morbidity which public health measures are supposed to prevent in so far as possible, as forcibly pointed out by Dr. Grulee in his letter to Senator Pepper, yet the new Wagner bill absolutely prohibits the assistance of public funds for the aid of the States in correcting faults and failures in the modalities for better health just enumerated.

Part B is in reality an abbreviated version of the Pepper bill dealing with grants-in-aid to States for maternal and child health services, including the care of crippled children, al-

though much of the detail of S. 1318 has been omitted. State plans must be approved by the Chief of the Children's Bureau who, with the approval of the Secretary of Labor, "shall make and publish such rules and regulations as may be necessary to the efficient administration of this part."

Title I, Part C, is entitled "Grant to States for Medical Care of Needy Persons." In approval and administration of plans, this part falls within the balivick of the Social Security Board. This is also the first instance in which a Wagner health bill has recognized the poor as coming within its social benefits.

The local administration of Part C is entrusted to a "single State public assistance agency." It is well to note the several administrative categories now being established under the bill, although the content of each Title and part consists of the distribution of medical services.

Should a "needy person," normally a ward of the State public assistance agency, contract a venereal disease, the question as to where and by whom he would receive treatment would become a ticklish one as between the United States Public Health Service and the State public assistance agency, to say nothing of the possible event that he might be a minor under 21, when even the Children's Bureau might have occasion to direct medical therapy according to the tenets of the Pepper bill! In any event, the prognosis as to cure may be jeopardized through the individual's misfortune not to fit snugly into any angle of the triangle which fences him in. Should the much touted rapid treatment be indicated, the slow motion involved in conflicting administration detail might well delay a cure.

Strange to relate, in Part C of Title I, relating to needy persons, an elusive ghost of a "means test" makes its appearance from behind the backlog of socialized medicine. On page 28, line 4, (8), appear the words: "provide that the State agency shall, in determining need for medical care (of needy persons) take into consideration (A) the requirements of individuals claiming medical care under the plan, and (B) any income and resources of an individual claiming medical care under the plan, which must be taken into consideration with regard to an individual claiming assistance under a State plan approved under the Social Security Act, as amended."

Title II, Prepaid Personal Health Service Benefits (health insurance), allocates the distribution of health services to the authority of the Social Security Board and the Surgeon General of the United States Public Health Service, the latter being directed to "perform the duties imposed upon him by this Act, under the supervision and direction of the Federal Security Administrator, and after consultations with the advisory committee hereinafter established (an entirely impotent body) as to questions of general policy and administration, and in consultation with the (Social Security) Board shall also have the duty of studying and making recommendations as to the most effective methods of providing personal health service benefits, and as to legislation and matters of administrative policy concerning health and related subjects."

The remainder of the National Health Act enumerates the details of governmental health insurance, administrative methods of accounting, and other minutiae for the consideration of which time is lacking.

Failing in the possession of a coordinating Secretary of Health of cabinet rank, the whole plan envisages confusion worse confounded, the functions of the practice of medicine being usurped by the Surgeon General of the United States Public Health Service, the officials of the Children's Bureau, and the Federal Security Board. One is reminded of the witches in *Macbeth* peering into their boiling pot as they watch the effervescence of their conglomerate broth and one may reflect the saying of the witches, "Double, double, toil and trouble; fire burn and cauldron bubble. The earth hath bubbles as the water has, and these are of them!"

The Pepper bill, S. 1318, is of more immediate concern to the members of the Academy. Any consideration of this piece of legislation should embrace a background of history, an exploration of which reveals much of interest. The Pepper bill repeats the oft made mistake of medical planners and social commandos in conceiving in secret legislative acts which have as their aim the utilization of the services of physicians as a vicarious outlet for their

presumably altruistic motives, if they may be called such—whether political aspirations or selfish considerations of a personal nature are implicated in this urge for social reform to be conducted at the expense of a learned profession—the question remains within the field of conjecture.

So far as the Academy of Pediatrics is concerned, no inkling of the legislation contemplated in the Pepper bill was brought to the attention of its officials until the morning of July 6, 1945, when a remark made to the writer, who was that day departing on vacation, by a member of the Children's Bureau gave notice that something in the way of maternal and child health legislation might be proposed by the Senate Subcommittee on Education and Labor.

One's suspicions were naturally aroused by published statements of officialdom in praise of the EMIC program and the desirability of projecting its principles into the postwar era, a forecast to which your Executive Board took vigorous exception some months ago, with a certain degree of prophetic wisdom which subsequent events have now justified.

The distinguished Senator from Florida in his speech introducing the bill bearing his name credits the inception and development of S. 1318 to certain groups of individuals whose testimony before his subcommittee and whose statements of record urged immediate and broad expansion of maternal and child health services. To quote the words of this speech:

"In administering the program of services for children under the Social Security Act, the Children's Bureau has sought the advice and counsel of outstanding physicians, social workers, and members of other professions who are authorities in the fields of child health and child welfare, and of citizen groups concerned with the problems of children. For the past year the Bureau's technical and general advisory committees have been reviewing and reappraising the programs in relation to present needs. Their recommendations, in turn, have been studied by the National Commission on Children in Wartime. Members of this commission include the chairman of the Bureau's advisory committee and representatives of labor, farm, women's, church, and professional groups.

"The present bill embodies the essential recommendations of this distinguished group of citizens, which has released a report entitled 'Building the Future for Children and Youth.'"

Senator Wayne Morse, one of the nine sponsors of the Pepper bill, writes to a physician in Oregon as follows: "As to S. 1318 it was drafted, so I understand, by the Women's and Children's Bureau. . . ."

The Associate Chief of the Children's Bureau in a report read to a joint meeting of the Advisory Committee on Maternal and Child-Health Services and Services for Crippled Children, on November 8, 1945, makes the following statement: "Today we are asking your advice particularly on certain legislative proposals (S. 1318) which have grown out of your recommendations on the expansion of the maternal and child health and crippled children's programs and those of the National Commission on Children in Wartime." Also the statement that: "Since the beginning of the subcommittee's work in 1943, the staff of the committee has kept in close touch with the Children's Bureau."

Your representatives have always pleaded for cooperation with other agencies in promoting the welfare of children and in collective agreement upon occasions where misunderstandings and differences of opinion were encountered. These features in promotion of harmony and conciliation have been conspicuously absent in the formulation of recent legislative proposals, although as late as one month before the introduction of the Pepper bill, in a communication to the Children's Bureau expressing appreciation for its aid to the Academy's postwar committee, the following closing paragraph was written: "It is the earnest hope of the Academy that through its State-wide organization and the assistance of its entire Fellowship of some 1,600 members, in conjunction with the valuable contributions of the United States Public Health Service and the Children's Bureau, this important study of child health needs, together with the facilities for meeting them, will provide a considered basis for future planning under the joint aegis of pediatricians in association with the Federal agencies vitally concerned in the health and welfare of children."

That this view was likewise entertained in theory on the part of officialdom, although subsequent events have indicated that it was largely theoretical, is shown in the statement of the Associate Chief of the Children's Bureau published in the *JOURNAL OF PEDIATRICS* of October, 1944, to wit: "Any detailed plans for children in the postwar period should be carefully formulated and widely discussed before they are crystallized into recommendations for legislation and should be of particular concern to the American Academy of Pediatrics as well as to many other professional organizations and citizen groups."

Analysis of the Pepper Bill, S. 1318

(Identical bills have been introduced in the House, namely:

H.R. 3927, by Representative Mary T. Norton of New Jersey

H.R. 3994, by Representative Augustine B. Kelley of Pennsylvania

H.R. 4059, by Representative Ellis E. Patterson of California)

On July 26, 1945, Senator Claude Pepper of Florida introduced the Maternal and Child Welfare Act of 1945, for himself and the following nine cosponsors: Mr. Walsh, Mr. Thomas of Utah, Mr. Hill, Mr. Chavez, Mr. Tunnell, Mr. Guffey, Mr. La Follette, Mr. Aiken, and Mr. Morse. The bill was referred to the Senate committee on Education and Labor.

Among the purposes of the bill, the Senator from Florida in his speech states: "This bill, which I hope will have early consideration by the Congress, *provides for gradual yet substantial expansion of existing State programs of child health and welfare instituted a decade ago under the Social Security Act. Step by step, over a period of the next ten years, the bill makes possible the enlargement and strengthening of these public services in accordance with the requirements of each State.*"

It may be said that no "existing State programs of child health and welfare initiated a decade ago under the Social Security Act" embrace the revolutionary principles advocated in S. 1318 but, on the contrary, the provisions of Title V of that Act provide government subsidies for three types of service, i.e., maternal and child health, crippled children and child-welfare, to beneficiaries *especially in rural areas and in areas suffering from severe economic distress*, with absolutely no provision that a free government "dole" be granted to every pregnant mother and to every child under the age of 21 within the United States including the District of Columbia, "or any Territory or possession of the United States."

The Social Security Act in no way provides for unlimited free medical services for "all mothers and children in the State or locality *who elect to participate in the program,*" provided that the mothers be pregnant and that the *children* be under the age of 21 years, an age limitation which may permit some beneficiaries to enter both categories with much consequent confusion to both patient and administrative authorities as to where they rightly belong!

The bill proposes to provide for the general welfare, thus possessing the cloak of constitutional respectability under Section 8 of the constitution which provides that the Congress shall have power to lay and collect taxes, duties, etc., to pay the debts and provide for the common defense and *general welfare* of the United States.

TITLE I

MATERNAL AND CHILD HEALTH SERVICES

Sec. 101. Page 1, line 9, and page 2, line 1 et seq.:

The bill states: "For the purpose of enabling each State to provide and maintain services *and facilities* to promote the physical and mental health of mothers during the maternity period, and of children, including medical, nursing, dental, *hospital, and related services and facilities* required for maternity care, preventive health work and diagnostic services for children, school health services, care of sick children, etc." Yet Senator Pepper (speech of presentation—page 4, paragraph 6) says: "The bill does not contemplate a construction program, such as is provided for in S. 191 or in similar provisions of other bills. But pending the passage of a broad program for construction of health facilities, State health departments

will be able to use some of the funds provided in this bill for necessary remodeling of facilities."

Page 2, lines 9 and 10:

Here is stated: "including demonstrations and training of personnel for State and local maternal and child health services." Does this mean the establishment of a kind of medical West Points as proposed in Congressman Dickstein's H.R. 713 or of State medical normal schools? Probably not. The training will be Federal and be provided by the Children's Bureau as directed on page 6, lines 1 and 2, wherein the Bureau is authorized to provide "opportunities for postgraduate training of professional and technical personnel." Where and how such training will be effected under the tutelage of the Children's Bureau is not further explained in the bill.

Page 2, line 13:

For the fiscal year ending June 30, 1946, there is authorized the sum of \$50,000,000, "and for each year thereafter a sum sufficient to carry out the purposes of this title." The absurdity of expecting this amount of government moneys to cover the necessities of all who would embrace the benefits of the Pepper bill, an unpredictable portion of some 3,000,000 mothers and some 40,000,000 children under the age of 21, need not be dilated upon, except to remark that after the first year the appropriations have no limit but the stratosphere in arithmetical digits. In this respect the bill is patterned on many previous legislative acts which are steered through the Congress in a manner similar to a poker game with a penny ante to begin with, but with an ultimate jack pot resembling a mountain of blue chips. The cost of this legislation would in the end enter the realms of billions, not millions if its proponents have their way.

Page 2, lines 15 to 19:

Herein appears one of the many inconsistencies in the bill. The individual States are authorized to prepare plans for *developing* such programs and *providing* such care and services (named hereafter) which must be *approved by the chief of the children's bureau*, but there are certain other "musts" associated therewith, the first and most emphatic "must" being admittedly the approval of the Children's Bureau.

The second "must" appearing in Sec. 103 (a), as well as in 203 (a) and 303 (a), respectively, prescribes what the State plans shall embrace and if complied with, according to the letter of the law laid down in this section, page 8, lines 5, 6, and 7 (the concluding paragraph), "The Chief of the Children's Bureau *shall approve* any plan which fulfills the conditions specified in subsection (a)." In this respect, the history of the EMIC program is replete with the conflicts and disagreements arising from the apparent authority of the States to originate plans and of the Federal government defining in detail the regulations under which such plans should have their birth and development.

Furthermore, to pass ahead for the moment and to visualize confusion worse confounded, one reads on page 8, under the heading Federal Advisory Committees, Section 105 beginning on line 9, the following: "The Chief of the Children's Bureau *shall formulate* general policies for the administration of this title. . . ." But previously in the bill [page 4, line 9, (4)] appears the directive that the State "provide for the administration of the plan by the State health agency. . . ." Who wins the tossup concerning this division of authority?

What about the "administrative policies" of the Children's Bureau which will govern the proposed Act? One might turn for an answer to experiences under the EMIC program and more especially to Information Circular No. 1, issued December, 1943, the title of which on the front cover is "Administrative Policies" but including within its covers what can only be construed as "regulations." The foreword states in part as follows:

"The Children's Bureau will use these policies as the basis for approval of the related portions of State emergency maternal and infant care plans. . . ." "The administrative policies of the Children's Bureau have been developed within the framework of the Congressional acts and the *regulations* of the Secretary of Labor, and in accordance with the intent of Congress as shown by the legislative history and as interpreted by the Bureau and by the

Solicitor of the Department of Labor." In one section containing six pages of the EMIC Administrative Policies, Minimum Regulation for Hospitals Participating in the Program, the word "must" appears three times, "should," three times, and "shall" appears forty-seven times!

Apparently, and in fact, the words "policies" and "regulations" are used conterminously by the administrative authorities of the Children's Bureau and the tremendous power of administrative fiat issued therefrom is admitted by the Associate Chief of the Bureau in a published statement entitled "The Children's Bureau and Postwar Planning for Child Health" [JOURNAL OF PEDIATRICS, Vol. 25, No. 4, October, 1944, p. 351], to wit: "The regulations of the Secretary of Labor governing allotments of funds to States for the EMIC program are published in the Federal Register and have the force of law." Violation of such policies and regulations by a long-suffering State will not only violate the law according to the above paragraph) but will instantly penalize the State by having the paternalistic purse snapped shut even if, in the administration of the plan (in theory formulated by the State) "there is a failure to comply substantially with *any provision required* by section 103, or section 203, or section 303, respectively, to be included in the plan, he (the Secretary of Labor) shall notify such State agency that further payments will not be made to the State under such plan, or . . ." and here follows a provision that the State will be put in 4F until it falls into line or has been rehabilitated (page 27, line 24 et seq.).

Let us return for the moment to the statement of the Associate Chief of the Children's Bureau already quoted, namely, that the policies of the Bureau have been developed within the framework of the Congressional Acts and the regulations of the Secretary of Labor, and in accordance with the intent of Congress . . . and as *interpreted by the bureau and by the solicitor of the department of labor.*"

This is written to draw attention to United States differences between bureaucratic and democratic procedures.

During the history of EMIC the writer has had occasion to bring to the attention of the Children's Bureau certain interpretations of its own and of the solicitors of the Department of Labor, which were obviously at variance with the wording of the law as viewed by the mind of a layman and not through the spectacles of a lawyer clouded by the snarls of legal technicalities. [JOURNAL OF PEDIATRICS, Vol. 26, No. 1, January, 1945, pp. 93 and 94.]

Now comes forward a champion of justice and right thinking who has much the same views and dares to express them in no uncertain terms. He is the Honorable Lewis B. Schwellenbach recently appointed as Secretary of Labor, formerly a Senator in the Congress and latterly a judge of the United States District Court of the State of Washington. Three days after taking office on July 1, 1945, he issued the following statement after conference with President Truman, who gave to it the presidential blessing as indicated in the closing paragraph of the press release, to wit: "The President indicated considerable interest and told him (the Secretary) that he would issue it (the order) from the White House."

Lewis B. Schwellenbach, the new Secretary of Labor, in an unusual move today served notice on his departmental associates that he expected them "to execute the laws" and not to ignore or attempt to circumvent them because they thought these statutes should have been written or interpreted differently by Congress and the courts.

The Secretary's action was disclosed in a White House statement which said that "with the approval of the President" Mr. Schwellenbach "has issued following general order No. 1":

"I am issuing this order now, before any specific instance arises so as not to subject anyone to embarrassment. Perhaps because my previous experience has been in the legislative and judicial branches of the government, I am peculiarly sensitive to the importance of this question.

"I must insist that in this department there is given full recognition to the fact that it is the function of this department to execute the laws. The duty of

an officer in this department is to accept the laws as Congress has written them and as the courts have interpreted them.

"The fact that he may think the Congress should have written or the courts should have interpreted a law differently in no case justifies him in ignoring or attempting to circumvent the law. I will expect full cooperation in this policy."
(*Washington Evening Star*, Tuesday, July 3, 1945.)

The writer has quoted at length the Secretary of Labor's criticism of the practices of some Federal departments in evidence of the fact that legislation is often subjected to the whims and fancies of those in authority in subordinate positions with evil results and would venture the observation that *of such stuff is bureaucratic government by regulation and regimentation composed.*

Page 2, line 25:

Here appears the wording "children under twenty-one years of age." When is a child not a child? Should the Congress so specify this designation of the word "child," it would expose itself to sharp criticism of having abducted through the draft, and perchance in some possible future military service law, mere children of 18 and 19; child labor laws must need be expanded in scope; the "age of consent" laws promptly revamped, while the study and practice of pediatrics should in all equity be enlarged to embrace a portion of geriatrics!

Page 3, line 15 (2):

One may wonder what are "the special problems of maternal and child health"—how are they to be ascertained and how qualified?

Page 5, line 19, Sec. 103:

Here is delineated the necessary attributes of a State plan in order to qualify for the receipt of Federal monies, subject to the limitation that they must be approved by the Chief of the Children's Bureau, although the latter *shall* approve such plans if in accordance with the requirements of this Sec. 103, whether the Chief likes them or not, all of which constitutes a sort of Washington Merry-Go-Round.

Now witness the beginnings of socialized Federal and State medicine.

Page 4, line 3:

Following the phrase containing a directive that the State provide facilities (although not a constructive program in the opinion of the framers of the bill) appear the words that services and facilities "furnished under the plan . . . shall be available to all mothers and children who elect to participate in the program." It is obvious that this feature of free Federal medical services extended to all who would embrace them constitutes a pilot exploration, insidious, revolutionary, and devastating in its effects upon the private practice of obstetrics and pediatrics, which, if enacted into law, would mean annihilation of both special branches of medicine and the liquidation of their adherents upon whose services the government depends for the distribution of its beneficences.

Herein goes into the discard any "means test" or financial qualification as to need which sets apart this proposed Act as one of startling novelty in the annals of Congressional legislation. Even the EMIC program was qualified by a general "means test" in that its benefits accrued only to the wives and infants of servicemen of the fourth, fifth, sixth, and seventh grades and to aviation cadets, the lowest paid classes in the Armed Forces. The legislative history of EMIC shows, also, that some appropriations committeemen questioned sharply the omission of a further means test in this measure.

Congress, together with the American people, believe in a means test. As a matter of fact, the Federal government insists upon the most widespread application of the means test ever required, namely, the income tax, which is based directly upon the financial situation of the individual.

Appropriations for the care of well children of working mothers under the Lanham Act are based upon a sliding scale of the means test and contributions are insisted upon from the parent embracing the facilities of these day nurseries.

From a Report prepared by Dr. Allan C. Butler at the direction of the Advisory Committees of the Children's Bureau assembled Nov. 8 and 9, 1945, the following is an excerpt:

(The committees in joint session)—Disapproval of paragraph (3), page 4, line 3 of Sec. 103. The following modification of that paragraph was favored: "(3) provide that as services and facilities are furnished under the plan they shall be available to all mothers and children in the State or locality *who are determined by the state health agency to be eligible and* who elect to participate in the benefits of the program, and that there will be no discrimination because of race, creed, color, or national origin, and no residence requirement";

The following explanatory paragraphs occur in the report of the subcommittee to the general meeting which adopted the above modification of a section of the Pepper bill relating to a means test:

"Among the 14 who favored this modification were members who were opposed to the means test in principle, but felt the above modification was essential to a tolerant consideration of such legislation at the present time.

"It was also felt by some that if the application of a means test was left to each State that the ultimate development through the Nation of efficient plans for medical care, such as considered here, would not be jeopardized. It was felt by others that this was a wholesome endorsement of State rights under such a program."

Several members of the Academy present advocated strongly that a means test be incorporated in the bill but were outvoted. The ambiguity of the phrase adopted (who are determined by the State health agency to be eligible) has been questioned even by the officials of the Bureau, especially in regard to its interpretation as to whether the directive is compulsory or only permissive on the part of the States. One might seriously criticize the clarity and the efficiency of such a modification of the bill if it were to be presumed to incorporate what is commonly known as a "means test."

Page 4, line 9, (4):

Note the words "provide for the administration of the plan by the State health agency . . . and for appropriate coordination of the plan with the general public-health and medical-care program of the State health agency: *provided*, that in carrying out the purposes of this title, the State health agency may develop agreements or cooperative arrangements with other State or local *public* agencies whose functions include the provision of services similar or related to the services furnished under the State plan." The word "public" used in this section is not akin to the "old tie schools of England" called public, but in reality private, but means governmental as opposed to private—a differentiation recognized on page 23, lines 16 to 19, also relating to cooperation "with State and local agencies, *public* and *private*, concerned with child health, education, child welfare, and related subjects."

This directive first quoted constitutes a prohibition (by omission) of agreements or cooperative arrangements with such private agencies as the Blue Cross, industrial indemnity sick benefit plans, prepayment plans of private organizations medically or otherwise initiated, but is at variance with and constitutes an inconsistency with the directive on page 6, line 3 et seq., stating that State plans will provide "such *use* of health centers, hospitals, clinics, and health service agencies, public and *voluntary*, as will achieve the satisfactory distribution and coordination of preventive, diagnostic, consultative, and curative services for mothers and children furnished by general practitioners, specialists, public health personnel, laboratories, and others." The first directive is prohibitive of agreements with private (voluntary) agencies, the second would seem permissive—but who knows what is meant by either except, perhaps, the interpretative ruling of a solicitor of the Department of Labor which may later appear as a Federal fiat in the columns of the Federal Register.

Page 4, line 20: "be made part of the State plan for maternal and child health services submitted in accordance with the provisions of Title V, part 1, of the Social Security Act. Senator Pepper in his speech (page 3, paragraph 5) says: "The bill, which I hope will receive early consideration by the Congress, provides for gradual yet substantial expansion of existing State programs of child health and welfare initiated a decade ago under the Social Security Act."

If that be the purpose of the bill, what is the necessity of usurping by new, over-all legislation, strikingly revolutionary in character, the orderly, legal functions of established governmental agencies which have accomplished much acknowledged good in aid of maternal and child interests throughout the States, but which have done so under careful, yearly scrutiny of regularly ordained appropriation committees of Congress after convincing justification of needs presented by officials of the bureaus involved?

Dr. Elliot's statement to the Executive Board on Monday shows this method of approach was given consideration by the Senate Subcommittee.

Page 4, line 6:

The State is commanded to provide "such methods of administration as are necessary for the proper and efficient operation of the plan" while on page 29, line 8 (Sec. 501), "The Chief of the Children's Bureau, with the approval of the Secretary of Labor, shall *make* (note the word *make*) and publish (it is presumed in the Federal Register, thereby having the force of law) such rules and regulations as may be necessary to the efficient administration of this Act." One might with unquestioned propriety ask Who's Who, under such ambiguous phraseology.

Page 5, line 7, (B):

The State is commanded to construct "standards for professional personnel rendering medical, dental, nursing, and related types of care or services, such standards to be *established* by the State health agency. . . ." EMIC and other experiences prove beyond peradventure that the Children's Bureau and not the State agencies have heretofore established such standards for professional personnel and for hospitals, in evidence of which we have quoted EMIC Circular of Information No. 1 with its array of "shoulds," "musts," and "shalls." This would answer the question Who's Who.

Page 5, line 13:

The State is directed to provide "such methods of administration of medical care as will insure the right of mothers and children, or persons acting in their behalf, "to *select*, from among those meeting standards prescribed by the State health agency in accordance with methods set forth in the State plan, the physician, hospital, clinic or health service agency of their choice (provided that the physician, hospital, clinic, or health service agency selected may refuse to accept the case), and where no such selection is made, the State plan shall set forth the method by which care will be *made* available." Herein, according to the proponents of the measure, lies the great virtue of the bill in possessing choice of physician, hospital, or clinic, but what are the limitations of such choice?

They are (1), only from among those meeting "standards" theoretically prescribed by the State health agency, but in the light of past experiences in the administration of EMIC and Social Security Title V, established by remote control in Washington by regulations alive with shoulds, musts, and shalls, which *have the force of law*.

(2) The bill graciously concedes that a physician, hospital, or clinic, may refuse to accept the case—i.e., not enter the "panel" of preferred and acceptable functionaries. What if the majority of physicians, in the language of Calvin Collidge, do not choose to run the gamut of the slings and arrows of outrageous fortune inherent in the bill? They are without the pale, and so are the beneficiaries of government largess if their chosen ministers of health, whom they may have always sought in times of illness, are not included among the elect.

(3) If the mother or child is thus bereft of medical aid from one of their choice, or if they fail to make a choice, the State will provide it, willy nilly, the element of choice having disappeared and that of compulsion by the State taking its place.

Page 5, line 24:

The question of adequate remuneration "for persons and institutions providing medical care and related services." Who is to establish what is to be considered as "adequate remuneration"? Past experiences with governmental experimental medical practice indicates that remuneration will be far from adequate and that the fee schedules will be established by

bureaucratic edicts which will remain as immutable as the laws of the Medes and Persians and that they will be fixed by remote control almost as distant from some State localities as Iran itself.

Page 6, line 9:

"Payments to individual physicians for care furnished under this title (shall be) on a per capita, salary, per case, or per session basis, or, in the case of consultations or emergency visits on a fee-for-service basis."

In the opinion of the majority of pediatricians (as ascertained by poll) and probably of most physicians, the four methods first named as repugnant to the principles of medical practice and destructive of the sound policy that the laborer is worthy of his hire.

Page 6, line 13, (4):

The key to the question of "ample remuneration" from governmental agencies, fully demonstrated throughout the years in their financial relationship to physicians and hospitals with which we are all familiar, is discovered in the wording of this paragraph, to wit: "Purchase of care from public or voluntary hospitals and other health service agencies included under the State plan (shall be) on a basis *related to cost* for providing such care." The same relationship, to judge from experiences under the administration of the EMIC program, will be applied to remuneration of physicians under S. 1318, namely, on a basis of *relationship only* to the value of the services they render, perhaps even to that of a second cousin twice removed.

Page 6, line 20, (8):

From past experiences, our compassionate sympathy should be extended to the State agencies who are required under this provision to "make reports (paper work) in such form and containing such information as the Chief of the Children's Bureau may from time to time *require*, and comply with such provisions as the Chief of the Children's Bureau may from time to time find necessary to assure the correctness and verification of such reports."

Page 7, line 3, (9):

The State plan must "provide 'cooperation' (of what nature the legislative proponent sayeth not) with medical, health, hospital, nursing, education, and welfare groups and organizations in the State."

Page 7, line 6, et seq.:

Herein, as in most medicosocial legislation proposed or in operation, commandeering and confiscating the intellectual ability of physicians, appears the red herring commonly dragged across the trail, to wit: the *advisory council* and the *technical advisory committees*, both appointed by the State health agency while both are sufficiently and well diluted with "other persons" or "other professional groups" to ensure the physician-membership a diminutive and ineffective minority.

The bill does not even possess the modest controlling interest vested in the selection of members from a "panel," as in the Wagner-Murray-Dingell bill, nor of the indulgence that any three members may demand a meeting of the advisory council as provided in the Hill-Burton bill, S. 191.

Time will not permit a discussion of the failures of "advisory committees," whose advice is eagerly sought when its presence in the administrative picture needs be painted large upon the canvass of cooperation, but in the passage of time such advice is usually relegated to an oblivion wherein its still, small voice disappears in the mist of remembrance only.

These same observations are equally pertinent to the Federal Advisory Committees (page 10, line 8) appointed by the Chief of the Children's Bureau.

Page 8, line 5, paragraph (b):

The bill directs that "The Chief of the Children's Bureau *shall approve* any plan which fulfills the conditions specified in subsection (a), which we have just analyzed. The Chief is unfortunately vested throughout other remaining sections of the bill with the right and prerogative of wielding an administrative tomahawk to effectively decapitate this particular directive in paragraph (b) relating to obligatory approval of State plans.

Page 8, line 8:

Under the title Payment to States. Methods of computing and paying Federal subsidies are outlined under the direction of the Secretary of Labor who will estimate such sums as are to be paid to the States on the basis of (A) reports and (B) "such other data as to such estimated expenditures, and such investigation as he may find necessary." Evidently the lengthy reports required from the State agency may not receive full credence.

Page 10, line 8: Federal Advisory Committees.

The Chief of the Children's Bureau shall formulate general policies (note the conterminous meaning of the words policies and regulations to which we have called attention) for the administration of this title after "consultation with (1) a conference of State health officers, and (2) an advisory committee composed of professional and public members." The dilution of an advisory committee by such public members who participate in the discussion of policies which are largely or purely medical in nature is certainly open to question, to judge by past performances of similar groups within the knowledge of the writer.

Page 10, line 21:

Here begins Title II, Services for Crippled Children. In wording and phraseology, both Title II and Title III (relating to child welfare services) are quite similar to Title I just considered.

In the first paragraph of Title II appears the directive that the States shall *provide and maintain* services and facilities for the care of children who are crippled, otherwise physically handicapped, or suffering from conditions which lead to crippling or physical handicaps. . . . Note again the directive to provide and maintain facilities, although the bill is claimed not to be concerned in construction of facilities. Note, also, the widening vista of the designation of what constitutes crippling, so that it may include, under Children's Bureau interpretation, such conditions as allergy, asthma, diabetes, nephritis, tuberculosis, syphilis, and other chronic diseases to which children are heir. But this is mere quibbling, as the Pepper bill provides medical care for all human beings under the age of 21.

Page 13, line 6, (4):

This paragraph permits agencies such as those of welfare, or State crippled children's commissions, or school boards, now administering crippled children's programs under Title V, part 2 of the Social Security Act, if approved by the Children's Bureau, to continue to function, but they must transfer their functions to the State health agency prior to July 1, 1950, which will necessitate many changes in present State laws.

Page 13, lines 21 and 22:

Repeats the wording of Title I that agreements or cooperative arrangements may be developed by the State agency with other State or local *public agencies*, to which attention already has been called.

Page 16, line 13, (10):

Provides (a) for a General Advisory Council "composed of members of the professions or agencies, public and voluntary, that furnish care or services under the State plan." The use of the word *or* in this paragraph, together with its use in a similar paragraph in Title I (page 7, line 8) actually permits the entire elimination of the medical profession from membership on the advisory council, if the State so desires to interpret the proposed statute.

Page 20, line 1: Title III—Child Welfare Services.

The first section, 301, contains a new feature regarding State plans as it authorizes payments in line 15 "to States for use by cooperating State public-welfare agencies which have developed jointly with the Children's Bureau, and had approved by the Chief of the Children's Bureau, State plans for developing such programs and providing such services and care." The word "jointly" now appears for the first time in the bill, to indicate a provision for joint State and Federal association in the development of programs.

Page 22, line 25, (g):

The control of the Children's Bureau is now made more complete and certain in a new wording, to wit: (the State) "provide such methods of administration as are found

by the Chief of the Children's Bureau to be necessary for the proper and efficient operation of the plan, . . ."

This, in reality, is the proper wording to explain what will actually be the remote control exercised by Federal bureaus over the States. The wording under Title I, page 4, beginning on line 24 (6) "provide such methods of administration as are necessary for the proper and efficient operation of the plan," repeated in exactly the same wording in Title II, page 14, line 5 (6), omits the clause "as are found by the Chief of the Children's Bureau to be necessary," but there can be no shadow of doubt but that the Title III injunction will in reality be the method employed in the similar and otherwise identical paragraphs in Title I and Title II.

Page 23, line 16, (8):

This paragraph introduces a new wording as contrasted with comparable paragraphs in Title I and Title II. It also for the first time uses the word "private" as applied to local agencies "concerned with child health, education, child-welfare and related subjects."

Page 27, line 16: Title IV—Administration:

Several constituent parts of this title have already been discussed, especially the one relating to failure of administration of a State plan to "comply substantially with any provision required by section 103, or section 203, or section 303."

Page 28, line 24:

This authorizes appropriations to enable the Children's Bureau to train "personnel for Federal, State, and local service" as previously pointed out.

Page 29, line 7, et seq. Title V—General Provisions:

Section 501 directs that: "The Chief of the Children's Bureau, with the approval of the Secretary of Labor, shall make and publish such rules and regulations as may be necessary to the efficient administration of this Act."

It would seem fitting to permit this title just quoted, which appears on the last page of S. 1318, to close this discussion of the bill as it reveals so clearly, honestly and without guile, who will make and publish the rules and regulations of an Act, which, if adopted by the Congress, has the potentiality of wreaking destruction upon the teaching and practice of obstetrics and pediatrics, and the possible alienation from the practice of medicine of their adherents, with consequent evil influence upon the welfare of the mothers and children of our country.

CONCLUSIONS

1. S. 1318, as introduced by Senator Pepper and as at present written, merits the unanimous disapproval of the medical profession, the members of which, obviously, will be commandeered to become the purveyors of medical care to all who will "embrace the benefits of the program." Those physicians who do not choose to participate will be left to their own resources to survive or perish in competition with government practice fortified with the bait of free service dangled before the consumer in the form of a Government dole.

2. The bill contains no definition of "physician," "practitioner," or "others," which implies that the high quality of medical care promised in the measure may be entrusted to cultists, quacks and charlatans, to the extreme detriment of its beneficiaries.

3. The bill, which in its initial appropriations mentions mere millions, will ultimately necessitate the expenditure of an amount in billions, as any fair-minded statistician may prove, thus adding to the burden of excessive taxation to be borne by the citizens of this country already groaning under the weight of a national debt of 262 billions of dollars.

4. The revolutionary changes in the practice of obstetrics and pediatrics will work actual detriment to the interests of mothers and children and thereby defeat the very purposes which this legislation purports to accomplish.

5. The centralized Federal control deprives the States of their constitutional prerogatives assured them by the founding fathers in the conduct of their own affairs.

6. The statistics of the draft, by twisting and distortion, have been used by propagandists to prove that the young of our nation under inadequate medical care grew up into

a band of weaklings. The realities are that the nation put into the field an army of 12 million men and women whose physical fitness was such as to win the greatest war in history, wherein our G.I. appeared rather in the role of superman than that of a physical wreck, to say nothing of the vastly greater army of those in production who were physically fit and able to contribute the sinews of war which led to victory.

7. Both the Wagner and Pepper bills defeat the very purposes for which they were evidently created, the bringing of relief in the form of adequate medical care to the indigent and medically indigent, as they both involve taking away of funds by excessive taxation from those least able to pay and contributing free doles to millions of persons financially in a position neither to ask nor to receive charity.

Within these bills is encompassed a Scriptural injunction long puzzling to the writer since his Sunday school days, but now made crystal clear through its interpretation by such legislation, namely, "To him that hath shall be given and from him that hath not, shall be taken away, even that which he hath!"

8. The Academy may register its approval of the enactment of the Pepper bill in its entirety, or, may express its disapproval of the proposed statute as now written.

9. The Maternal and Child Welfare Act of 1945, if it be the wish of the Academy, may be endorsed as one of the objectives of which it wholly approves, but with reservations concerning the question of economic need of its beneficiaries, the artificial age limit of childhood as fixed by the bill, the lack of authority and method of appointment of advisory committees, the proposed allocation to a Bureau in the Department of Labor of authority to develop and direct such an extensive medical care program (Butler Report, Children's Bureau, November, 1945), and in respect to other features not in accordance with the principles and beliefs of the membership of this body.

Such an endorsement on the part of the Academy would be in keeping with its expressed opinions relating to the first National Health Act of 1939, as evidenced by the following resolution adopted in annual meeting after a consideration of that proposed Act:

Resolved, 1. That the American Academy of Pediatrics approves in principle the objectives of the National Health Act as it relates to children, but recommends that the Senate Committee on Education and Labor give further detailed study to its provisions, *with the counsel and advice of practicing physicians* and professional organizations who together will form the instrumentalities through which the success or failure of the Act will be determined.

2. That the American Academy of Pediatrics, regarding the provisions for maternal and child welfare, favors the use of public funds to provide such services *to those groups of the population unable to pay for medical services*, to the end that the standards of medical care may be maintained at a high level among such groups.

10. At the Annual Meeting of the Academy held in St. Louis, November, 1944, this body unanimously authorized the formation of a committee on postwar planning which, with the aid of the Children's Bureau and the United States Public Health Service, was empowered to conduct and is now engaged in conducting a study of the needs of children in every State and locality, with the end in view of meeting these needs, not by revolutionary Federal fiat based upon assembly-line methods, but by orderly, democratic processes to be evolved after the completion of this study and survey. As to how these aims may be accomplished without trespass upon the civil liberties of the American people, the Academy has expressed the following opinion:

"The financing of such extension of medical services for children cannot be reduced to any one simple formula. It may be provided for by direct payment to the physician by or for the individual receiving the services, by the extension of voluntary insurance plans on a local level, by compulsory insurance plans (extension of social security), by direct taxation on a local or State level, by Federal grants-

in-aid from tax funds as a joint responsibility of local, State, and Federal government. The determining factor should be the situation existing at the local level and undoubtedly a combination of the various methods of financing may be needed in many places."

In conclusion, it may be thought by some that the content of this report smacks of belligerency, but we would point out that the nature of these legislative acts engenders a spirit of antagonism among those who have at heart the interests of pediatrics.

We regret, more than we can express, the necessity for recording certain severe criticisms of the acts of co-workers in behalf of the welfare of children to whom must be accorded a sincerity of purpose and an honesty of conviction no less earnest than our own.

We of the Academy should like to be taken into the confidence of proponents of new legislation affecting our interests and prerogatives and which would also command our good offices in order to guarantee the success of any future child welfare planning, a function with which we are now intimately and officially concerned.

The Fellowship of the Academy must have, and now is provided with, the opportunity to express its views concerning pending legislation, not only for the guidance of those who officially represent it and must speak in its behalf during interim periods, but also for the equally to be desired guidance of those who would frame and enact legislation in the interest of children.

JOSEPH S. WALL, Chairman.

THE CHAIR.—You have heard this excellent report of this Committee on Pending and Proposed Legislation on Child Health. It is now open to discussion.

DR. ALLAN M. BUTLER, BOSTON, MASS.—Dr. Wall's description of the Pepper bill in which he has given free play to his imagination and presented his personal reactions to the bill was well done as is almost everything Dr. Wall does. He has effectively utilized the technique of humor, ridicule, and insinuation in a manner which I think would almost make Dr. Morris Fishbein jealous. I think it is to be regretted that Dr. Wall did not have the time to outline the good as well as the bad in the Pepper bill. Rarely, as remarked by Dr. Sinai, is something all white or all black. I am sure that Dr. Wall does not think the Pepper bill all black. Perhaps his limitation in time prevented him from a more searching analysis of the Pepper bill. This is unfortunate, in that his description of the bill has hardly presented the Society with an objective description which will help the Academy objectively consider the bill at this meeting.

And yet at this meeting it is essential that the Academy objectively consider this proposed legislation. For there are two things, it seems to me, which this Academy cannot afford to do, because of its responsibility in educating pediatricians and in defending the quality of pediatric medical care. One is in a blanket manner to condemn the Pepper bill without presenting to the public the specific reasons for so doing. The other is that the Academy cannot afford to dodge the issue of a frank and critical discussion of the Pepper bill.

I had hoped in the course of this meeting merely to present thirteen concrete reasons why the Academy should not approve of the Pepper bill as it is now written. But before doing so it seems to me almost essential that someone in a very brief manner correct some misconceptions and outline the opportunity for good that might come out of a proper modification of the Pepper bill. First, I was a little disappointed at Dr. Wall's suggestion that the Advisory Committee should not have members representing the public, for after all, is not this medical care in terms of financing and use, the public's medical care? Dr. Wall also uses the phrase "free medicine." Today we have free medicine for those people who cannot afford to pay for medical care. It has to be free to such people. It is not only free to such people, but we physicians give it freely without remuneration. In the Pepper bill, properly modified as a basis of reasonable legislation to cover the need of the people who cannot afford to pay for their medical care, there probably will be no more free medicine in the terms of the recipients than exists today. The medicine given recipients will be given by physicians not freely but with adequate remuneration of the physicians. I do not know how many

people in this room have stopped to think of the increasing burden that charity is placing on the physician. Those of us who spend the major part of our time in institutions see the increasing burden that charity is placing upon the people whom we are asked to serve.

In a sense the Pepper bill is almost like the Federal Reserve Act. If properly modified, and we should be able to see that it is properly modified, it makes the resources of the national government available to cover the costs of illness to such of the population as we think it ought to be made available. In doing so it has to set up certain rules and regulations to protect the public in the utilization of public funds. In this respect it is like the Federal Reserve Act. In itself there is nothing in the Pepper bill that need change the manner in which any individual physician or groups of physicians or institutions render medical care. It is definitely concerned with the collection and distribution of the costs of medical care and the problem of remunerating the physician. There is nothing in it that in itself is inimical to the doctor's individual freedom in rendering professional service. The Academy because of its prestige in maternal and child care can certainly see to it that the practice of physicians is not unduly infringed upon by such legislation.

I would like now to present the thirteen reasons why I think the Academy should not endorse the Pepper bill as now written. I have put them in the form of a resolution, so that the Academy, if it sees fit, may conveniently take action concerning them. [Published in this issue of the JOURNAL, p. 390.]

Two explanatory remarks seem pertinent. First, there are two very important reasons why fee-for-service should not be excluded. Dr. Sinai has mentioned one; namely, that under the American system of general practice some doctors do both general practice and specialist or consultant practice. In paying such doctors on a capitation basis, definition of what will be included under capitation payment and what will be included under specialist payment presents a difficult problem. The second reason is that under such a plan a great many physicians, perhaps the majority, will not be seeing under the provisions of the bill enough patients to give actuarial coverage of varying incidence of illness. Therefore, you have no right to ask physicians to accept a method that denies a reasonable distribution of the risk when seeing so small a group of patients. The second explanatory remark pertains to supplemental charges. Stipulation that no supplemental payments can be made is important, if we as physicians are going to be able to insist that adequate remuneration be provided under such legislation. As soon as you may make provision under such legislation that doctors or hospitals can demand supplemental payments you are almost invariably bound to establish lower rates of remuneration than if no supplemental payments can be made.

DR. PARK J. WHITE, St. Louis, Mo.—At one of the meetings yesterday, criticisms of health agencies were made. It was apparent that with the depression which is going to come—and this country has not hit the low levels of the countries of Europe—we can see a need for Federal funds. If we are going to accept Federal funds, whether for school health programs, programs for contact infections or other activities, we can also see a need, as indicated in the survey, for trained personnel. This the government, particularly in the Children's Bureau and the Public Health Service, has available. To condemn government participation out of hand is not the intention, I believe, of Dr. Wall or of any of the rest of this group.

With regard to the definition of childhood, we have seen that the draft was open to "men over seventeen," and now we hear of "children under twenty-one." With the government as with the rest of us, a good deal depends on what we actually want.

Changes are coming and they are coming by way of insurance system not necessarily by compulsory legislation. I believe as a result of the survey which is about to be undertaken, we shall see the next move is one which will bring about certain changes in medical practice. Also this group and others will show those who are bringing in new methods that they will have to include in their deliberations the advice of the doctors themselves.

DR. R. L. J. KENNEDY, ROCHESTER, MINN.—My discussion of the report of the Legislative Committee is based upon a summary of opinion regarding S. 1318 as expressed in replies to letters to the members of the Academy in Minnesota asking for their opinions.

Replies were received from nearly half of the members in the State. No opposition was expressed to the broad objectives of the bill although one or two expressed the feeling that the bill should be killed, without making any specific mention of its alleged purpose.

The concept that the government, be it State or Federal, must assume responsibility for furnishing complete health and medical services to all pregnant mothers and to all children regardless of the economic status of husbands and fathers is obviously not shared by any of the members from whom written replies were received. On the other hand, a plan which does not provide for assumption by the government of financial responsibility of those able to pay their pay and at the same time provides for high-class medical care for those unable to supply themselves with it, would receive favorable consideration. It was suggested that any plan should recognize the necessity of both private and public health services as we now have private and public schools.

Control of any plan which may be adopted should be bested in the several states rather than in a federal agency according to those who commented on this aspect of the bill.

One member expressed the view that "it is not possible to practice good medicine, or honest medicine, under government control; that the practice of medicine and especially of pediatrics requires not merely skill but great patients and self-sacrifice and that these virtues will be killed by government medicine."

These represent, very briefly, the objections, both moderate and extreme, to the principles involved and to provisions of the bill as expressed by members from Minnesota. Time does not permit mention of many criticisms of specific provisions which were offered.

Since doctors are not accustomed to formulate legislation, it is not surprising that few suggestions were received which can be designated as constructive criticism. One member offered the suggestion that, "the Chief of the Children's Bureau be made responsible to a board consisting of state health officers, members of the medical profession, chiefly pediatricians, and lay members. The proportion of one-third each would be satisfactory." Another suggests that "services be limited to those whose financial status is such as to render it impossible for them to pay or to whom meeting a large expense would bring undue hardship." One states that "many more people could provide the services of a physician himself on a personal basis if other costs were defrayed."

What can be offered which will be helpful in attaining the goal which we all seek? Following suggestions which have come from some of our state members, it would seem right and proper (1) to forward with all expedience the work of the Committee of Nine, and (2) to seek modifications of S. 1318 which will be based upon the findings of this committee, which will take cognizance of the opinions of a majority of members of the Academy as expressed here and elsewhere and which will conform so far as possible with the ideas of those who must be greatly concerned with the administration of any plan, the American Medical Association, the Association of State and Territorial Health Officers, and then place behind it the full weight of the Academy in support of its passage.

DR. STANLEY H. NICHOLS, ASBURY PARK, N. J.—May I respectfully disagree with Dr. Park White that the point is whether or not we will approve the setting up of a Federal health program for the population. As far as this Academy is concerned, it seems to me that the thing in our minds which is most important in the national picture is whether or not we set up a *means* test, whether in pediatrics or anywhere else; in other words, are we prepared as an Academy or as a medical profession to start medical service for all at public expense? I think there are two common grounds with which we can begin. The Committee on Cooperation with Government and Medical Agencies proposed a national program, calling for cooperation between the American Academy of Pediatrics and the American Medical Association, the United States Public Health Service, and the Children's Bureau. This program is ready whenever the Academy wishes to use it.

One of the great men of this country, Eric Johnston, president of the United States Chamber of Commerce, is a very wise man who has spent his life adjusting difficulties. He says this, which we can take to heart: "When two groups disagree and cannot find a common ground, we should make a survey around the table until we find a common ground and then resume negotiations."

Dr. Park has laid before you the "Maryland State Plan" which provides that (1) the medical profession of Maryland, dentists, nurses, hospitals, (2) industry, labor, farmers, and (3) public agencies get together and provide care of the indigent and medically indigent, which is a very logical program, we admit, for the low income group, and no saner proposal for cooperation has come to my notice. I would suggest that at the business meeting tomorrow the American Academy of Pediatrics approve the Maryland Plan.

Secondly, I called to Dr. Park's attention last night, and Dr. Sinai referred to it today, that a national insurance plan has been passed by the American Medical Association at its meeting in December. Dr. Brunk of Michigan and Mr. Mannix, who is the national president of the Blue Cross, offered a second plan, namely, "to have a national health congress made up of these same components as in the Maryland State Plan." The House of Delegates of the American Medical Association directed the Council on Medical Service and Public Relations to set up a "National Health Congress" composed of representatives of the American Medical Association, the American Dental Association, the American Hospital Association, pharmacists, nurses, etc. If that "National Conference" can be brought into being it will be a great step forward by the American Medical Association. I recommend that first we endorse the state plan of Maryland and that we help participate in a national health congress and that we endorse the idea that "those that cannot pay for medical services," be so provided for. That is the common ground on which the American Academy of Pediatrics, the American Medical Association, and all concerned can participate. I recommend it as a basis for discussion tomorrow for this group.

DR. H. KENT TENNEY, JR., MADISON, WIS.—I believe I am safe in saying that my remarks represent, with fair accuracy, the opinions of most of the pediatricians in Wisconsin as well as of those individuals charged with the responsibility of administering existing child health programs.

We, in Wisconsin, believe that there are certain aspects of medical practice where individual physicians, local agencies, State agencies, and Federal agencies can and should pool their efforts. And we believe that such pooling of efforts can result in definite benefit to all concerned. But it is our unalterable contention that the policies and practices that govern the activities of these agencies should be determined locally. We feel that, in spite of fairly frequent visits to the State by representatives of Federal bureaus, we still know our conditions and our problems better than anyone remote from the scene can ever know them. And it is this complete and utter abrogation of state and local rights which it calls for that makes bill S.1318 or any reasonable facsimile thereof so very unpalatable to us in Wisconsin. When one considers the endless overlapping and duplication of existing programs that this bill provides for it is no wonder that many of our administrators view it with alarm.

While it is true that many of us believe that under the provisions of this bill the practice of pediatrics as we have known it will be considerably altered, I would like to emphasize that our opposition to the bill does not stem from a fear of losing our practice but rather from a conviction that the bill will lead to so much confusion and resentment as to hamper seriously maternal and child health activities. We do not, for a minute, contend that our programs are perfect. On the contrary, they need considerable amplification and we are developing plans for that purpose. But that to place such complete control over the practice of medicine, down to the "smallest political unit" of every state, in the hands of the Chief of one bureau is the way to improve our services is what we emphatically do not believe. And, while our relationship with the Children's Bureau has on the whole been a cordial one, the memory of some past experiences in trying—and sometimes unsuccessfully—to fight off some "do this or get no money" directives leaves us anything but happy over the prospects of what could take place under the provisions of bill S. 1318.

It has been said that this bill put the health of children in the same category as their education. Now this ideal of making health available to all children is one with which nobody has any quarrel. But, our system of public education and the provisions of bill S. 1318 are so diametrically opposed as to make any such comparison entirely untenable. Every school district elects its own school board which decides its own policies with a minimum of participa-

tion by even the state officials. But bill S. 1318 would completely reverse this system and require the Chief of the Children's Bureau to formulate all rules, and regulations for the medical, dental, "and related services" of every political unit of every state. And, may I repeat, it is this feature of the bill, this complete abrogation of State and local participation in the formulation of policies, that forms the basis for much of our opposition and convinces us that our Child Health Programs would suffer rather than benefit by its enactment.

If the Congress would allot to the State Board of Health, or other responsible agency, its share of the proposed appropriation, and require that body to be guided by a committee representing medical, dental, hospital and lay groups, then it would be possible to develop plans, tailored to fit local conditions, and free from the administrative strings that are always attached to Federal funds. Only in the case of bill S. 1318 the strings have grown to be more like rubber bands that will snap your money out of your hands if you do not watch out.

Lest anyone should consider that Wisconsin occupies a position that is mainly obstructionist in nature, I would like to say a few words about our plans for improving maternal and child health in our state.

We believe that it is little short of suicidal for organized medicine to sit on its haunches and howl about proposed plans without proposing some positive plans of its own. In line with that belief, then, the State Medical Society's Committee on Maternal and Child Health has drawn up some plans which we think will serve as a workable starting point. The thesis which underlies all of our planning is that a broad and continuous system of education is fundamental in the development of any sound health program. It is not enough for medical science to develop new techniques and new knowledge of disease. These advances must be constantly available to the profession and public alike. But it is really not enough that these advances be merely available; for we must admit that all too often they must be practically stuffed down the necks of some of our professional brethren. If our educational program includes the wise and wide dissemination of sound knowledge as to what constitutes good pediatric practice, then parents will demand good and adequate care for their children and thus force the complacent physician to brush up or get brushed off. So, as one of our educational activities, we contemplate the creation, within the framework of the State Board of Health, of a full-time position as Director of Education.

It will be the duty of this Director in conjunction with the medical schools, schools of nursing, hospitals, medical societies, etc., to organize and conduct a continuous program of postgraduate education. He will also, in conjunction with such organizations as the American Legion, and the National Congress of Parents and Teachers, organize a continuous program of lay education.

It has often been said that one of our most pressing needs is an increased emphasis on pediatric teaching. With the return of Dean Middleton from Service, plans are rapidly going forward which envision a great expansion in the whole field of preventive medicine.

As other aids in our program, it is planned to double the number of public health units in the state and to enlarge greatly the staff of Public Health nurses.

To do all this it would of course be very nice to have some Federal funds. But rather than submit to the complete domination that we see sticking out of every angle of bill S. 1318 we shall try to carry on alone.

THE CHAIR.—As there is no further discussion, I will declare the session adjourned. (The session was adjourned at 12 Noon.)

Annual Business Meeting

Jan. 18, 1946

The annual business meeting of the American Academy of Pediatrics was held in the Book-Cadillac Hotel, Detroit, Mich., on Friday, Jan. 18, 1946. The meeting was called to order by the President, Dr. Joseph S. Wall, at 10:10 A.M.

THE PRESIDENT.—The first order of business is the conferring of Pediatric Awards. Dr. Joseph H. Stokes, a member of the Committee, will make the award on behalf of the Academy.

DR. STOKES.—After arriving in Detroit I received a letter from Dr. Graham Ross saying that he would be unable to be present and asking me to act as chairman. Unfortunately the Mead Johnson Award, which is for outstanding achievement in the past ten years and consists of one prize of \$1,000 and a second prize of \$500, is not to be awarded this year. Dr. Ross requested that I read the report he drew up.

Report of Committee on Mead Johnson Awards

The Committee appointed by the American Academy of Pediatrics on Awards recommended that for this year no award should be made.

The reason for this decision is that it is generally felt that there has been no work of sufficiently outstanding merit published by those who would qualify for the award.

It has, therefore, been decided that it would be better to postpone the award for this year, in order to maintain the standards of investigative work which have been shown by the previous recipients.

S. GRAHAM ROSS, Chairman.

Report of Committee on Borden Award

The Borden Award is a yearly award of \$1,000, together with an appropriate medal, for that pediatrician of any age who, in the opinion of the Committee on Awards, acting for the Academy, has performed work of outstanding merit in research in nutrition of infants and children. This is the second year that such an award has been made.

In contrast to the prolonged discussion and the difficulty of decision in the case of the now postponed Mead Johnson Awards, in which an age limit has been designated by the donor, the Committee's decision in respect to the Borden Award was prompt and unanimous.

Of men in the field of research in medicine there are a few, a very few, who, by great skill, untiring effort, and well-controlled but far-sighted imagination in their chosen field of investigation have erected milestones in medical progress which will stand forever. The recipient of this year's award has pursued his chosen field of rickets in this manner, and with the work of years has erected such a milestone. He once facetiously termed the field of rickets his particular saloon in which he spent a large portion of his time in quiet retirement. It may be added that this saloon contains a few choice spirits, and one may always expect a kindly and gracious welcome.

Of equal importance in the field of research has been his exceptional facility for stimulating and fostering the spirit of investigation in young physicians, not alone in his own school of medicine, but of those young men and women with whom he has had contact throughout all fields of medicine.

On behalf of the Chairman of the Committee of Awards, Dr. S. Graham Ross, and in the name of the American Academy of Pediatrics, I present the Borden Award to a great teacher and investigator, who has earned the affectionate regard and esteem of all who have known him, Dr. Edwards A. Park.

JOSEPH STOKES, JR.

DR. PARK.—When this kind and very pleasant thing happens to a person it causes him to look back on himself. I think it is a very dangerous thing to look back on one's self and Dr. Howell, the late Professor of Physiology at Baltimore, once told me it was so painful to him that he never did it. When I look back on myself in regard to the investigations which I have done, particularly the investigations on rickets, I am aware that nothing I have ever done to rickets has been of first merit. I can mention on my fingers the great achievements in rickets, the discovery that rickets was a vitamin deficiency disease, the discovery that ultraviolet light was curative of rickets, and the discovery of a new vitamin, vitamin D, and the fact that the fetus could be irradiated with ultraviolet light, the great contribution of the late Dr. Hess and Dr. Steinbach, and the discovery that rickets as ordinarily encountered was a low phosphorous disease, a discovery that was made by Dr. Howland, Dr. Kramer, and coincidentally by Dr. Lynch. I might go on mentioning other milestones. My part has been very small. I was concerned with the work I did in collaboration with Dr. McCollum,

and Dr. Shipley pointed the way that phosphorus was very intimately associated with rickets. Recently it was thought that rickets was due to calcium deficiency. I remember a very amazing anecdote of Dr. Leonard Finley who was visiting Dr. Howland. They entered into an argument one evening at dinner as to whether rickets was produced by calcium deficiency or phosphorous deficiency. Dr. Finley contended it was calcium; Dr. Howland, phosphorus. Those of you who know Dr. Finley know that he is a very persistent Scot. Dr. Howland told me his one thought was how to get him to bed. He finally stood up and said, "What can I do for you?" Dr. Finley replied, "I would like another cigar." I think probably Dr. Howland was right in the discussion, although Dr. Finley knew that he was.

I accept this award with all humility, feeling that it really is an expression of appreciation of effort, and that effort in right directions, that is, the appreciation of the value of countless little things.

THE PRESIDENT.—The next order of business is the consideration of applications.

THE SECRETARY.—The following lists of applicants have been approved by the Executive Board. [Published in this issue of the JOURNAL, p. 347.]

I move that the action of the Executive Board be approved on these applicants.

(The motion was seconded and carried.)

THE PRESIDENT.—The next order of business is the request for emeritus membership.

William N. Bradley, Philadelphia, Pa.

Guy I. Bliss, Long Beach, Calif.

Howard C. Carpenter, Philadelphia, Pa.

James Dunn, Davenport, Iowa

I move that the action of the Executive Board be approved and that these gentlemen be granted Emeritus Fellowship.

(The motion was seconded and carried.)

THE PRESIDENT.—The Executive Board also elected to Honorary Membership, Dr. Donald Paterson of London, England, and to Associate Membership, Dr. Franklin Henry Top, Detroit, Mich.

(It was moved, seconded, and carried that the action of the Executive Board be approved.)

The next order of business is the reading of the President's address. [Published in this issue of the JOURNAL, p. 249.]

THE PRESIDENT.—The next order of business is the report of the Secretary and the report of the Treasurer. [Published in the February issue of the JOURNAL, pp. 217 and 221.]

THE PRESIDENT.—The next order of business is an obituary for Dr. Cooley by Dr. Henry Helmholtz.

THE PRESIDENT.—The next order of business is the report of the Regions. [Published in February issue of the JOURNAL, p. 218.]

The next order of business is the confirmation of the action of the Executive Committee concerning the report of the Committee on Fetus and Newborn. [Published in the February issue of the JOURNAL, p. 224.]

THE SECRETARY.—In the report two questions were asked, one by Dr. D. Lesesne Smith concerning change of State laws in regard to eye prophylaxis with a view to the use of penicillin in place of silver nitrate. The other by Dr. Jerome Glaser, concerning the definition of the newborn period. The Secretary was instructed by the Executive Board to write the Chairman of the Committee asking that it continue its investigations concerning the use of penicillin in place of silver nitrate and report at a future meeting. In answer to Dr. Glaser, the Committee on Fetus and Newborn recommends:

1. That the term "neonatal" rather than "newborn" be used to cover the period after birth that Dr. Glaser asks us to define.

2. That, for the sake of uniformity, the first month (first 30 days) should limit the neonatal period. This may be regarded as an official definition since it has been agreed upon by the Children's Bureau, the American Public Health Association, and the Bureau of Census (the Registrar, Bureau of the Census, U. S. Department of Commerce, Vol. 4, No. 2, February 15, 1939).

I move that the action of the Executive Board be approved.

(The motion was seconded and carried.)

THE PRESIDENT.—The next order of business is the report of the Committee on Redistricting the Academy. [Published in this issue of the JOURNAL, p. 352.]

DR. MARTMER.—For the last few years it has been evident to the Executive Board that representation on the Executive Board was becoming a one-sided affair. That was true because of the manner in which the Academy was divided at the time of organization. At the time it was organized the natural division was eastern, southern, middle western, and far western states. As time went on with the tremendous increase that has occurred in the membership of the Academy, as I have already noted, the representation became equally distributed. For that reason the President, on the recommendation of the Executive Board, appointed a committee consisting of Dr. Goehle and myself and we were to submit plans for making as nearly equal representation of the Academy as possible. Probably all of you have all seen copies of the report of the Committee. The recommendations of the Committee are as follows:

1. That the Executive Board submit to the membership the proposal that the Academy redistrict Regions I, II, III, and IV into eight (8) districts based upon an equal number of members in each district.

2. That the districts be represented by a district or Regional Chairman with all the duties and responsibility now held by a Regional Chairman.

3. That nominations and election of such Regional Chairmen be done in the manner now prescribed in the Constitution.

4. That the term of office of a District Chairman be for a period of eight (8) years.

5. That the Executive Board be empowered to make all necessary changes in the By-Laws of the American Academy of Pediatrics to accomplish the redistricting as proposed in this report.

We have a slide to show the proposed redistricting of regions by actual numbers. Whereas Region I, which constitutes the New England states, New York, and as far down as Washington, at the present time has 725 members, Region II comprising what is commonly known as the southern states has 326 members, Region III, the middle western states has 468 members, and then going out to the extreme western states, and this divided by the Rocky Mountains, we have a total of 209 members. Under the process of redistricting, District 1 would have 188; District 2, 210; District 3, 198; District 4, 198; District 5, 226; District 6, 221; District 7, 236; District 8, 212. District 9, which is at the present time Region V, consisting of the Latin-American countries, will continue as it is and there will be no change in the components of the District, it will simply be a change in name. As time progresses and if and when the membership in the Latin-American countries increases, then further subdivisions of that District may be undertaken.

At the time the Academy was organized it was felt that much of the work of the Academy would be carried on through the Regions, that is, the regional meetings would provide a common meeting place for those states in this particular area at which problems peculiar to the area would be considered. That stage in development has apparently pretty well passed. Much of the work that was formerly regional in nature has become national in scope. Some of the work which in the formative period was on a regional basis is now being carried on on a state basis. The function of the Region as such was perhaps diminished as the Academy itself has moved forward. At the present time the Regions still have a function in that they have, prior to the onset of hostilities, formed a means of providing a clinical meeting for those individual members who were not always able to attend the national meeting, primarily because of its place of meeting. In other words, if the

meeting were held in the far east it would be difficult for the membership on the extreme west coast to attend, and so there was the feeling that they wanted a clinical meeting at least once a year and the regional meeting served that purpose. There was one very great difficulty in at least two of the Regions, that was the question of finances. Whereas, Regions I and III could provide clinical meetings that were self-sustaining and self-supporting, Regions II and IV were under considerable hardship in that respect. If this proposed redistricting is carried out, it is the thought of the Executive Board that while the annual meeting will continue to be held in the fall and the location will continue as in the past to be in various parts of the country so that from time to time it will be in cities accessible to the membership and not in one particular place, that if the meeting were held in the extreme east, a clinical meeting in the spring of the year would be held at a point which would be accessible to those members who because of the great distance involved and traveling to the annual meeting in the fall, would not be able to attend the meeting unless additional meetings were held. It might be necessary to hold two additional meetings, such meetings to be put on through the efforts of the Secretary as are the annual meetings, which because of their nature are much more likely to have a larger attendance and may be actually self-supporting. It means greater effort and more work on the part of the Secretary and his Staff, but as the Academy grows it is natural that such labors should increase.

The redistricting is proposed and it is the desire of the Executive Board that it be very thoroughly studied and considered, and on the basis of such consideration that it be voted upon at the next annual meeting. Is there any question about it?

DR. BORDEN VEEDER.—I think it is a very good idea. One thing I would like to have thought given to, that is, the proposed Executive Board. Is one new man to go every eight years? I would like to express the thought that it might be wise to have the term of office for four years with two members elected every year, with the privilege of re-election. I am not making a motion.

DR. ALLAN BUTLER.—As one goes through the minutes of the Academy one is impressed with the fact that we should lower the age limit of members who are acting on committees. I think the younger members have a definite feeling that they are not allowed to participate in committee discussions which concern a great deal the policies of the Academy. For instance, the Committee on Legislation is composed of very wise individuals but there is not a member on the committee who is under 60. Therefore, those members are determining the legislative policies of the Academy which will not affect those individuals but will affect the members thirty years younger. I would like to see more young men on the policy-forming groups of the Academy.

DR. HELMHOLZ.—I came to the same conclusion as Dr. Veeder did and I had the privilege of discussing this with the Chairman of the Committee. He seems favorably inclined and if he wishes to have some action on this which may help, I shall be glad to make a motion.

THE SECRETARY.—The question of membership on a committee is one that depends on activity and not on age. We have continually tried to find younger men who would do the job. That has been going on for five or six years. If those who wish to have younger men will give suggestions we will meet those suggestions with an open mind and an open heart. It is difficult to find younger men who will do the job. The older men have been tried and we know what they will do. We would like to have younger men. There has been a continual change in the Executive Board along that line. I think the whole tendency in the Board has been to discover younger men who will do the work. The fact is we have to get the work done. If we can get younger men to do it, we are willing to put them on.

DR. VEEDER.—I move that a change be made in the Executive Board in the redistricting program, that the members serve for four years, two members to be elected each year. (The motion was seconded by Dr. Garrison.)

THE PRESIDENT.—As I understand it, the members of the Executive Board should be elected for four years rather than as they are now.

DR. VEEDER.—It states in the report that they will be elected for eight years.

THE SECRETARY.—Would you like to add the privilege of re-election once? We do not have anyone on the Executive Board for longer than eight years. You could say with the privilege of one re-election.

DR. VEEDER.—I accept that.

DR. FRANK VAN SCHOICK, JACKSON, MICH.—The proposal is for nine districts. It would seem easier if members of the Executive Board were elected for three years.

THE PRESIDENT.—This proposal must go over one year. These amendments must be submitted to the Executive Board and then brought before the members at the November meeting. Any motion will be to suggest for the consideration of the Committee that two district chairmen will be elected for a term of four years. Dr. Van Schoick suggests three years.

DR. MARTMER.—There is only this to be said. There has been more and more a feeling on the part of Region V that they want to be considered exactly as the other regions, and it might be well from the standpoint of policy to treat all regions on exactly the same basis. With nine members of the Executive Board and a three-year tenure of office, it would provide a stable Board.

DR. VEEDER.—That will be satisfactory.

THE PRESIDENT.—Do you accept nine members for a three-year term and re-election for one term if the District desires?

THE SECRETARY.—Three members would go off each year and their successors would be appointed for terms of three years, with the privilege of reappointment at the end of that time for one year.

THE PRESIDENT.—You have heard the motion that for the consideration of the Committee, it is suggested that district chairmen be appointed for a three-year term each, with the privilege of reappointment for a term of the same length. (The motion was carried.)

I wish you would think about Dr. Martmer's proposal on redistricting.

DR. HARMON TREMAINE, BOISE, IDAHO.—I would like to say a word for those of us who live in the West. When a man from Denver goes to Seattle he travels 1,600 miles by rail. I would, from a selfish standpoint, rather be left in the midwest district.

THE SECRETARY.—These districts are only administrative districts. They are not the districts which hold meetings. The old method of holding meetings will be discontinued and all meetings will be from the central office. There will be two or three meetings a year. That is a point which must be remembered. There is no intention whatever of using this redistricting as anything but as administrative policy, and the future meetings will be determined by the location of the annual meeting. Then we will have other meetings in the sections of the country which are not in definite connection with the annual meeting. That is what it calls for.

DR. EUGENE B. SCHUSTER, PITTSBURGH.—If redistricting is for the purpose of administration and the districts do not hold meetings, and out of the administrative divisions come responsibilities, are our representatives going to take the responsibilities? How are the representatives going to be chosen?

THE SECRETARY.—Heretofore it has been the custom of the Executive Board to ask the regional chairmen for the recommendation of two from each district so that they can take their choice for associate chairman. The regional chairman has been elected on the recommendation of the Nominating Committee of the Academy and the associate chairman usually is selected from two names that are presented by the regional chairman after consultation with the state chairmen in his region and the vote of the state chairmen. That has been the custom in the past. I suppose that in the future according to this plan the nominations will come from the Nominating Committee and unquestionably I should think would be on the recommendation of the state chairmen within any given district. I do not think that the methods have been set up.

DR. GENGENBACH.—I was going to raise the points that the states of Wyoming, Colorado and New Mexico are on the other side of the mountains. Originally Colorado was put in Region IV, but our problems are associated with the Middle West. As far as the number is concerned, there are 17 in Colorado, 1 in Wyoming, 4 in New Mexico, which would only take off 22 members from that district.

THE SECRETARY.—It is only for a matter of administration and for no other purpose. I cannot see that it makes any difference to the state what group it is in.

DR. VEEDER.—A practical point comes up, the question of the Nominating Committee. The Nominating Committee has been a committee of four, one from each region. What is the plan of handling that in the future? It was not discussed. I have served on the nominating committee a couple of times. The nominating committee has polled the state chairmen of each region for their choice as to officers and the committee has taken the selection. How are you going to handle that in the future?

THE SECRETARY.—That has not been discussed.

DR. PAUL W. BEAVEN, ROCHESTER, N. Y.—How is Canada redistricted?

DR. MARTMER.—On the basis of the plan as it has been set up, Quebec will be in District 1, Saskatchewan and Manitoba in District 6, British Columbia in District 8. Puerto Rico will be in District 4, Hawaii in District 8. Alaska will be in District 8, as soon as we have a member elected from that country.

DR. HOWARD J. MORRISON, SAVANNAH, GA.—I would move that one member of the nominating committee be from each of the nine districts. That would include a representative group from the entire Academy.

(The motion was seconded and carried.)

THE PRESIDENT.—We will now present resolutions from the Executive Board.

DR. LEE FORREST HILL.—Your Executive Board presents the following resolution adopted on Jan. 17, 1946:

The American Academy of Pediatrics in annual session at Detroit, Michigan, January 15-18, 1946, after careful consideration of proposed legislation in Congress as it relates to child health services reaffirms its resolution as adopted at its 1939 session, namely:

"That the American Academy of Pediatrics, regarding the provisions for maternal and child welfare, favors the use of public funds to provide *such services to those groups of the population unable to pay for medical services*, to the end that the standards of medical care may be maintained at a high level among such groups."

The Academy of Pediatrics does not favor the use of Federal funds for those able to provide good medical care for their own resources.

The Academy directs the attention of those considering proposed legislation to its fact-finding study of child health services now in progress which, at its conclusion, should assist in the development of sound programs at state levels based on demonstrated needs.

Pending the completion of this study, it is recognized that urgent needs exist in some states that should be met in the immediate future. To this end the Academy recommends that additional Federal funds be made available for grants-in-aid to the states under existing Maternal and Child Health and Crippled Children's programs of Title V of the Social Security Act.

The Academy would welcome the privilege of sending its representatives now or at any time to confer with those responsible for the preparation of legislation pertaining to child health.

I move the adoption by the Academy as a whole of these resolutions.

(The motion was seconded by Dr. Gengenbach.)

DR. STRINGFIELD.—I would like to call attention to the next to the last paragraph. It says, "Maternal and Child Health and Crippled Children's program of Title V of the Social Security Act." I would like to add to that "as amended in 1939."

THE PRESIDENT.—That is the usual legal wording. I am sure Dr. Hill will have no objections.

DR. STRINGFIELD.—My reason for adding that is that some members confuse the Social Security Act with the EMIC program.

DR. BUTLER.—I would like to have one point clarified and that is in regard to the publication of the various papers read and comments made yesterday morning in the session on postwar planning and medical economics. There were two papers read yesterday, one by the President and the other by Dr. Sinni. Are the remarks pertaining to the discussion to be published?

THE PRESIDENT.—The papers and reports are published in the JOURNAL. I will ask Dr. Veeder.

DR. VEEDER.—We publish all the minutes of the Academy meeting that come to us from the official stenographer. We do not consider it the function of the JOURNAL to amend what the members say at its meeting. The Secretary, Dr. Grulee, assures me, Dr. Butler, that the minutes will include all the discussions.

THE SECRETARY.—I have not talked much on this situation. I have put out only one piece of information regarding it as to my opinion. It is not because I have not felt. I feel we are at the turning point of American pediatrics. I think the situation is a very, very serious one. At the meeting in St. Louis we were assured by Dr. Eliot that there will not be any future legislation coming from the Children's Bureau based on the EMIC program. I know from Dr. Eliot that she does not consider the present Pepper bill as being the child of that EMIC program. In the point of time and purport the Pepper bill is the child of the EMIC program. In the St. Louis meeting I talked with her and Dr. Helmholz. She asked me why I was so in opposition to the EMIC program. I told her that I felt that it was the entering wedge for legislation along this line and that I would not be in favor of such legislation. Dr. Helmholz said he felt the same way, and that it would be unfair to the profession to do it that way. I think Dr. Helmholz, knowing him as I do, puts the same interpretation that I do and that Dr. Eliot does. To me the situation is far more serious than that. It means eventually, say what you please, that the medical men and pediatricians of this country will not run pediatrics in this country, will not take care of the child as they have in the past, that it will be done by the Children's Bureau. If the Children's Bureau were to consult the pediatricians and take the words of the practicing pediatricians as directives in their effort, I would not so feel. What has happened in the Pepper bill—I did not find this out until this meeting—I found it out because Dr. Eliot came to this Executive Board. There is in Washington a lay group in close affiliation with the Children's Bureau. I do not know the name of that Committee. That Committee had two doctors on it, Dr. Helmholz and Dr. Baumgartner. As far as I know Dr. Helmholz and Dr. Baumgartner did not consult with other pediatricians in the matter of preparation of this bill. If we are to have that type of cooperation from the Children's Bureau, I am against cooperating with the Children's Bureau in frank language. If the Children's Bureau can come clean with us and can say so and so, all right. I want to say this. I have been on the Advisory Board of the Children's Bureau for over ten years. I have never seen that anything I said that was opposed to the views of the Children's Bureau had any weight. I had to say this because I feel that I should say it so as to let you know how deeply I feel on the whole situation. It has spoiled the meeting for me. But I feel I should tell you how deeply I feel on the whole situation.

DR. HELMHOLZ.—May I make one or two slight corrections on what was said? Drs. Stevenson, Eastman, and myself were on the Executive Committee of the Commission on Postwar Care. The report of the Executive Committee was submitted to all the members of that larger group. Among those to whom it was submitted is our President. He had opportunity to have objected to anything in that communication. I do not believe there was any report from him as to objection to anything as outlined by the Committee.

DR. HILL.—Anyone who wants to discuss this resolution may do so.

Dr. BUTLER.—I would like to refer to two points. Dr. Grulee as a member of the Advisory Committee of the Children's Bureau has made a statement which suggests that the Children's Bureau has not accepted advice rendered by physicians on this Advisory Committee. As a member of the Advisory Committee and as a physician I would like to state my impression that rarely has advice been given by the individual physician member of the Advisory Committee of the Children's Bureau that that advice has not been accepted or received generous consideration.

The second point I would like to make pertains to the feeling that the Children's Bureau has not lived up to its agreement that the EMIC program would cease with the cessation of the war. Dr. Eliot in her statement before the committee concerned with postwar planning either in St. Louis or Chicago was asked specifically the question, would the EMIC program cease with the war and would the experience of the EMIC program be carried on to programs pertaining after the war. Dr. Eliot said, "I can say definitely the EMIC program will cease with the termination of the war. I, as a member of a government agency concerned with the improvement of medical care of women and children, cannot say that the experience derived from the EMIC program will not be utilized as a basis for planning for better care of women and children." I think many members of the Academy forget that Dr. Eliot's job for the government is planning for improvement in maternal and infant care. To accuse Dr. Eliot as being unfair in utilizing information derived from the EMIC program is totally unfair. I can see no justice in the statement that experience with the EMIC program is being unfairly applied in the Children's Bureau's planning for the future. I can see no fairness in the statement that Dr. Eliot has not stuck to her words.

THE SECRETARY.—I would like to answer those questions because they are questioning what I said. In one of the meetings at Washington of the Advisory Committee, every doctor and every nurse said that in the future in any planning or any action which affects the medical care of children the medical profession should be consulted. That was the action definitely taken by this group on the Advisory Board. Every doctor voted in favor of that as did every nurse at that meeting. So far as I can see, if the Children's Bureau had anything to do with the Pepper bill, the medical profession was not consulted in the formation of that bill. I may be wrong in my interpretation of what impression Dr. Eliot intended to give us at St. Louis. If I am wrong there are a great many other men who were at the meeting and who were present at the time when this was said, who gained an entirely different impression from Dr. Eliot's talk. I know Dr. Eliot made exactly the statement that Dr. Butler credited to her at the meeting of the Advisory Committee in Washington because I called up the question and asked if it would be used as a wedge in future legislation. The answer was exactly as Dr. Butler has given. I had the impression that at St. Louis she said it would not be used as an entering wedge in future legislation. There are men in this audience who told me they understood it the same way. There is always a chance for misunderstanding. I do not know that I have anything further to say on that, but I think those are the answers to Dr. Butler's objections.

DR. PARKE WHITE.—It is my impression that the committee of physicians that had most to do with the preparation of the Pepper bill is the Committee of Physicians for the Improvement of Medical Care, a remarkably fine group.

THE SECRETARY.—How many physicians were there on the committee and how were they constituted?

DR. WHITE.—There was some overlapping of membership. There are some pediatricians on it. Knowing the constituency of that committee I expected to join it myself. That does not mean any official connection between the pediatricians and the preparation of the Pepper bill. I really do not know what the doctors have had to do with that except I do know that this one committee—there may be others—is the committee of physicians for the improvement of medical care and not to be confused with the committee for the extension of medical practice. I have gone along with Dr. Butler's impression of the Pepper bill. The amount of approval or disapproval is submicroscopic.

DR. BUTLER.—As a member of the Committee of Physicians for the Improvement of Medical Care (there are in this room at least three members) I would like to correct a statement that was just made. The Committee as a committee was not consulted in the preparation of the Pepper bill. To my knowledge neither Senator Pepper nor the actual individual who wrote the bill, one of Senator Pepper's assistants, consulted the individual members of the Committee of Physicians for the Improvement of Medical Care. After the writing of the bill various members of the committee were asked to express their opinion concerning it. The Committee in making a statement concerning the Pepper bill criticized the bill very largely as to the thirteen points I mentioned yesterday in criticizing the Pepper bill. The Committee, therefore, does not approve the Pepper bill. I think there are some misunderstandings on the part of many individuals concerning the manner in which Federal legislation is introduced. The initial draft is apparently utilized by Congress as a means of discussion and as a means of obtaining information, so that two, three, four, and five drafts of the legislation can be made with continued discussion and the ultimate legislation represents the opinion derived by discussion of these various drafts presented to Congress. Congress must have done that with a certain amount of wisdom derived from experience, and I know not what that wisdom is. It is obvious if you want to get action on a matter you make progress by having something concrete to discuss, to which you can direct criticism. We have had recent experience in relation to several bills before Congress establishing the National Science Foundation. Unless several drafts of proposed legislation had been written and proposed, some kind of concrete information could not have been obtained from Senate hearings held pertaining to such legislation. I am sure it would have been very difficult to obtain legislation which might be translated into concrete proposals to be submitted to the entire Congress unless an initial draft was presented for discussion. The Pepper bill is the initial draft. The Pepper bill will not be considered by any committee in Congress unless many groups have been asked to express their opinion. The Pepper bill will not get to the floor of Congress until medical men and pediatricians are given an opportunity to express their opinions. Therefore, I do not think we should get too excited over the feeling that someone has presented an original draft that is to be the basis for discussion.

DR. VEEDER.—I had not intended to speak on this but I want to stand by Dr. Butler in his statement that the Committee for Improvement of Medical Care had nothing to do with this. A statement is being prepared showing disadvantages of the Pepper bill. I think we are making a little mistake. First of all, the thing we are interested in is better medical care for children. That is the primary thing. There has been a bill introduced in Congress to provide medical care on a basis that we do not believe will provide better medical care for children. I think we have every right to object to it. I think it is a waste of time to sit here and discuss the Children's Bureau. What we have to do is to discuss what is in this bill. If we take simply the negative attitude toward the matter we will not get anywhere. We have no right to go as individuals or as the Academy or as Academy representatives before a committee in Congress and simply say, as was the experience of the A. M. A., "We object to this." We have to have reasons why we object, and much more, we have to have definite recommendations as to what should be included in any bill passed by Congress in legislation for children. It seems to me that that is important and the thing we should do.

DR. McQUARRIE.—So that there will be no doubt as to who the third member of the committee is, I wish to speak. I accepted a place on this committee because I do not think medical care is as good as it might be. I do not like the attitude of the A. M. A. in many things. I do not go with it in taking the stand alluded to by Dr. Veeder—we will not play ball. We will organize a society that it against everything. A society that is opposed to everything that the government does is to me ridiculous. I am not in favor of state medicine and regimentation. I am not in favor of taking this legislation as it is passed today. I am in favor of improving medical education of doctors. I think then we should improve medical care and to provide general practitioners with good scientific training. I think we as medical men in full-time positions should provide good training for our students. My chief interest is a discussion of research, avoiding anything that is destructive. I have the

impression going about this country as a guest speaker that pediatricians in private practice are doing as fine service as we would expect all members of the Academy to do. All the people we cannot take care of must be taken care of, which means care coming from taxation. That is where some national organization, the Children's Bureau or some other, must set the machinery. None of us on the committee are in favor of destroying medical practice and having a great number of practitioners working on small salaries. I hope that statement can be made.

DR. JULIUS H. HESS.—For a point of clarification as far as the stenographer's notes are concerned, Dr. McQuarrie used the term A. M. A. as a society that is opposed to everything.

Dr. McQUARRIE.—As a matter of fact I am a great admirer of the A. M. A. I worked on the Council for ten or twelve years. I am in favor of many fine things they do, but I do not favor their standing aside and objecting to everything that is done. I like what they did in one committee, the name of which I cannot recall.

DR. HESS.—That is the National Physicians' Committee.

DR. LENDON SNEDEKER, BOSTON, MASS.—As a member of the younger married set, so to speak, I am interested in this legislation from its general character. The discussion yesterday seemed to center entirely on the Pepper bill and since this was closely related to child welfare services, I wonder what the Executive Board's attitude was toward the introduction of this legislation and its specific attitude as to the Pepper bill. I thought the criticism offered by Dr. Butler yesterday was timely.

THE PRESIDENT.—In the report of the Legislative Committee three bills were concerned—the hospital bill, the Murray-Wagner-Dingell bill and the Pepper bill.

DR. RATHBURN.—I would like to ask a question, why the people who are interested in setting up legislation are not willing to extend the social security bill. I find in this resolution it states, "The Academy recommends that additional Federal funds be made available for grants-in-aid to the states under existing Maternal and Child Health and Crippled Children's programs of Title V of the Social Security Act." Why is it not possible for those who wish to do any work for children to extend the facilities and the amount of money that comes to us under the provisions of the social security bill? It seems to me the two things to object to are the lack of a means test and the unlimited amount of money that is spent by the Pepper bill. Would we not accomplish more if we could have Congress spend the amount of money extending the provisions of the present maternal and child health and crippled children's program?

THE PRESIDENT.—The Department of Labor has given thought to extending the social security program but was in favor of the Pepper bill.

DR. ROGER KENNEDY.—I presume that all that will come from this meeting today is an expression of opinion that is to represent the opinions of the majority of this group. I know very little about child psychology. I was taught if I had a child with temper tantrum, to advise the parents to walk off and let him be, that he would eventually get over the tantrum. If this meeting is to gesticulate under a show of emotion, the American Academy would be taking the part of the tantrum child, and the officers, the parents, who represent us, will walk off. I think we have to be careful unless we go off that way. In order to bring it to a head I would like to ask this question. I have been thinking since yesterday about the resolutions of Dr. Butler. I wonder if they would be unfair to the group I represent, that is, the members of the Academy in our state. I think the import of what is put forth points to an effort on our part to delay action on the bill in its present form to allow time for modifications to be considered, modifications that might be elaborated not only by our group but also by other groups. It seems to me that we might consider the points Dr. Butler offers as resolutions. They might influence modifications, which would be the best way of handling this rather than this complicated resolution which covers all resolutions.

DR. HILL.—It seems to me that if we attempt to translate the resolution into the feelings of all of us, we will be here for the next two weeks. It seems to me the thing

on which all of us on the Executive Board were agreed was that we have some thought about a means test on a state level. That, I think, springs from the Academy group, and that is the point of this resolution. If you want more resolutions after this to cover other shades of viewpoints, that is O.K. Our feeling was that here was a definite stand that a committee could or could not make. I prefer that a vote be made on this resolution.

DR. E. B. SCHUSTER, PITTSBURGH.—I would like to tie in with what Dr. Kennedy was saying. The question before the house is the recommendation made by the Committee. You can accept it or reject it. The question is, does it express the will of the majority of the Academy? I have been wishing to sit still, but I cannot quite do so, because I think what is presented in the resolution is nebulous and not creative. It does not tell the people who are going to plan legislation anything about what we think ought to be done, anything detailed about what is before them. It does not do anything more than object in a very broad way without dealing with the objectives that have been brought out and that ought to be dealt with. My own opinion is that we should deal with the real issues before us which are pretty well crystallized.

THE PRESIDENT.—I call attention to the fact that one of the resolutions state that the Academy would welcome the privilege of sending its representatives now or at any time to confer with those responsible for the preparation of legislation pertaining to child health.

DR. BUTLER.—My reason for asking whether the remarks made by the speakers would be recorded was that yesterday afternoon a great many individuals came to me saying, "Those thirteen specific critical comments on the Pepper bill should be recorded." Certain people asked me if at the meeting this morning I would resubmit those criticisms. The statement which is now before us is a very good introductory statement. One could, if it seemed desirable, merely end that statement by saying, "The Academy submits the following specific criticisms of bill S. 1318, and because of these objections the Academy cannot approve, or disapprove, S. 1318." The Academy disapproves S. 1318 because of the objections given. That can be appended to what I think is a very good resolution.

DR. PARK.—May I subscribe to Dr. Butler's view. It would seem to me that that would be a wise addition.

THE PRESIDENT.—Would Dr. Butler care to introduce these thirteen criticisms?

DR. BUTLER.—I move as an amendment that there be added to the resolution as now before us a section which will present the Academy's specific criticisms of the Pepper bill as now written, and that the thirteen points mentioned yesterday be the basis of the specific criticisms but that the final form of the specific criticisms be determined by a committee to be appointed by the President with power to act.

(The motion was seconded by Dr. Veeder.)

DR. FRANK VAN SCHOICK.—I think it will occur to those present yesterday that the President treated those objections more in detail than did Dr. Butler. I would suggest that the thirteen points suggested by Dr. Butler be not the only basis for this Committee. As a matter of fact, the President had more objections and more in detail.

DR. W. L. CRAWFORD, ROCKFORD, ILL.—I think most of us have the same idea in mind. We would not be here in Detroit if we did not want to do everything we can to help child care. No one can argue with the statement that what we want is better child care. We will argue whether the Children's Bureau has not done the best they can as they see it. You may not like my work, but I have done my best. I think we will all agree that the Children's Bureau has done a very fine work. I think we should consider the passage of the resolution. The question before us is this, is the Children's Bureau going into pediatric practice and general practice? If so, should we wish to work with the Children's Bureau as was done during the war? We, in turn, should like to work with the Children's Bureau, but we should not like to work with the Children's Bureau as a competitor in the small towns and hamlets. I am taking time which is valuable because that is the viewpoint of the general practitioners. I think from my own viewpoint I would like very much to see this resolution voted upon and voted upon favorably. There

is no reason why after digesting this at our next meeting or another meeting, if we find we have been a little bit stubborn, we cannot vote differently. At present I would favor the passage of this resolution.

So much for the main resolution. I would like to make a few remarks about the papers yesterday. Dr. Wall's paper was very long, it was obviously one-sided. Dr. Butler's suggestions were very good. The Pepper bill is now in committee. I think the amendment of Dr. Butler's should be passed as an entirely separate thing and not considered a part of this resolution.

DR. -----.—You have approximately one-sixteenth of the representation of the Academy here. I feel that the majority of the Academy feel that this resolution is what they want. In reference to the amendment, I feel the Committee should not be given power to act, because they will not have the expression of the Academy to act on. Let the special committee draw up what they want and let them send it to members of the Academy by mail and let them get a true expression. It is a tremendous piece of work, but it is the only way we can get a true impression.

THE SECRETARY.—I would like to ask if he would regard a vote as based on the total membership or on the number of votes cast for this resolution and how he would regard those who offered certain changes which undoubtedly will be offered in case a mail vote is taken. I think it is almost impossible to get anything definite out of a mail vote. I think it would very much reduce the effect of such a resolution, not because I do not want to get the reaction of the members of the Academy by a mail vote. The members will not vote yes or no, they will want to make suggestions in these resolutions. I know every man has his own ideas on the Pepper bill and why he does not like it. I do not believe a vote by mail can be carried out successfully.

DR. -----.—I feel the most important thing before the Academy is that we have certain objections to what is in the Pepper bill and other bills. I feel the resolution carries enough weight and that the Academy is strong enough with the Children's Bureau to make its weight felt. I believe the resolution carries that point.

DR. GARRISON.—The stenographer has the points Dr. Butler made. Should we not have Dr. Butler read them? I am opposed to Dr. Butler's amendment. If Dr. Butler wants a different group to assist, I doubt that that is wise.

THE PRESIDENT.—The Chair has a copy of Dr. Butler's thirteen points.

DR. VAN SCHOICK.—I think the resolution states in general the objections. If there is a special committee appointed to go over this, we should have confidence in this committee. Therefore, I offer a substitute motion taking the place of all other motions that we accept the resolution as presented by Dr. Hill.

(The motion was seconded.)

DR. PARK.—I suggest that Dr. Butler withdraw his amendment and present it as a second motion.

THE PRESIDENT.—Dr. Butler, would you be willing to withdraw your amendment?

DR. BUTLER.—With the consent of the seconder I withdraw the amendment.

(The motion to adopt the resolution was carried.)

DR. BUTLER.—I now re-introduce my motion as read yesterday.

(The motion was seconded by Dr. Park.)

THE PRESIDENT.—I think it is only fair that we should hear the criticisms read.

The Academy in defending the interests of pediatricians and the public cannot afford to ignore the Pepper bill or to condemn it without mentioning the specific reasons for so doing, therefore the following specific criticisms of S.1318 are offered:

1. The bill as now written states that services and facilities furnished under the state plans are to be available to all mothers and children who elect to participate in the benefits and therefore denies to the States the right to determine eligibility.

2. The bill excludes fee-for-service as a means of paying practitioners for service rendered.

3. The bill makes inadequate provision for paying groups of physicians or institutions for professional services rendered.

4. The bill does not specify that professional personnel, groups, or institutions do not accept supplemental payments. This may lead to a low scale of professional remuneration under the bill that would undermine scale of payments, etc.

5. The bill endorses the Children's Bureau as the most suitable administrative agency of this major step in a National Health Program without assuring integration of the administrative functions and health services under this bill with other health activities of the Government.

6. The bill does not satisfactorily define the Federal or State advisory committees as regards personnel, method of appointment, advisory and policy making roles or manner of giving authority to the record of consultations with and recommendations to the Administrators at Federal and State levels.

7. The bill makes no provision for variation in remuneration for service according to the differing costs pertaining in various states.

8. The bill makes no provision for the prevention of arbitrary requests on short notice by the Federal Administrative Agency for reports from the State Health Agencies and similarly arbitrary requests by the State Health Agencies for reports from those rendering services.

9. The provisions for handling claims are unsatisfactory.

10. The bill fails to specify adequately reference to coverage of dental care in appropriate portions of the bill.

11. The bill makes no adequate provision for the protection of the well-organized and integrated teaching services on which the future quality of medical care is so dependent.

12. The bill makes inadequate provision for the support and encouragement of research pertaining to the improvement of maternal and child health services and medical care.

13. The bill makes no provision for assuring that State plans be expanded at rates that do not exceed available administrative and professional personnel and resources and that assurance against too rapid expansion be considered as one of the criteria of approval of a State plan by the Federal agency.

For these reasons the American Academy of Pediatrics believes that the Maternal and Child Welfare Act of 1945 (S. 1318) does not represent the best form of legislation for the purpose for which it was written.

DR. J. M. BATY.—May I ask Dr. Butler his recommendations on the formation of a committee.

THE PRESIDENT.—That was not in the part just before us.

DR. BUTLER.—That is not necessary. Those thirteen points were read before 300 members yesterday.

THE PRESIDENT.—The Chair will rule that Dr. Butler did not include the committee, therefore it is not included in the motion.

(The motion was carried.)

THE PRESIDENT.—The Chair will recognize Dr. Van Schoick under new business.

DR. VAN SCHOICK.—In the State Chairmen's meeting the night before last, when the child study program of child health services was presented to the state chairmen, it occurred to me that there was considerable doubt in the minds of many state chairmen as to how this survey would be received when they returned home. I have had the unusual opportunity in so far as Michigan is my home, that the Council of the Michigan State Medical Society is now in session. Yesterday I spent the afternoon with several members of that Council and asked them if they would give their approval of the survey in Mich-

igan. They asked many pertinent questions and they did not approve of many of the problems. They recognized that the object of the survey was well stated. While this is not official, it comes from the Executive Council of the Michigan State Medical Society, and I can say that they have given their approval for the study in Michigan. Without the consent of each state medical society the survey will not be approved. Therefore, I think it would be of interest to you state chairmen to take this information back to your own state, that Michigan has given its approval to the study provided it participates in it and has adequate staffed groups so that the organized medical profession will have some access to the information derived. I feel that the Academy owes to the medical profession in general a leadership which we have so far only attempted. I think that the time is coming for the Academy to appoint a representative committee that brings up just this parenthetical thing that Dr. Kennedy mentioned with temper tantrums, that the fault is all the child's; I think you will recognize that the fault is not all the child's but perhaps the parents'. I draw the analogue that maybe the parents should be represented as well as the child. I therefore offer this motion: that the President appoint a committee of not less than twelve members to review the data compiled and accumulated by the Committee on the Study of Child Health Services, with instructions to bring to the membership of the Academy recommendations for a plan of action to implement the objectives of the Academy as expressed in the resolution, based upon the findings of the survey being conducted by the Committee on Study of Child Health Services.

(The motion was seconded.)

DR. BUTLER.—I happen to be a member of the Committee concerned with the Academy survey. At the committee meetings we have had several discussions concerning the ultimate utilization of the factual data obtained. Here at this session Dr. London was very anxious that the ultimate utilization of the data obtained be specified. I think I represent the opinion of the committee correctly, that it is unwise to make a commitment concerning the utilization of the factual data except in the broadest terms until the factual data has been accumulated and until it has been appraised and until it has been adequately set in motion. I think it would be unfortunate to appoint a separate committee to determine how the facts are to be utilized before we know what they are. I think it would be far wiser to instruct your present committee which is concerned with the survey to amplify for the Academy such opinions as they now have concerning the possible utilization of the facts resulting from the study.

QUESTION.—How large is the present committee?

DR. VAN SCHOICK.—The Committee consists of three from the Academy, three from the American Pediatric Society, and three from the Children's Bureau.

DR. HUBBARD.—All nine members are members of the Academy.

THE SECRETARY.—The Committee of nine went out of existence and the committee as constituted represents an Academy committee and as such they are all members of the Academy.

(A rising vote was taken and the motion was lost.)

THE PRESIDENT.—The Secretary will read two amendments to the by-laws.

THE SECRETARY.—Article III, Section 2, page 11, the words *with the exception of Region F* be deleted.

Article III, Section 4, Page 11, following the word "President," *annually* be inserted followed by a *comma*.

In the same section, page 12, top line, a *comma* be inserted after "Regional Chairmen." I move that we adopt these amendments.

(The motion was seconded and carried.)

THE PRESIDENT.—There are certain resolutions to be read.

THE SECRETARY.—The following resolutions are presented:

Be it resolved, that the American Academy of Pediatrics expresses its sincere appreciation to the local members in the Detroit area and to Dr. Edgar Martmer for the splendid cooperation in the planning and conduct of the annual

meeting held at the Book-Cadillac Hotel, January 15 through 18, 1946. The Academy especially commends the Clinic Day as an outstanding presentation.

Be it resolved, that the American Academy of Pediatrics expresses its sincere appreciation of the superior manner in which the Detroit Hotel Association handled the hotel registrations for the annual meeting of the Academy held January 15 through 18, 1946.

Be it resolved, that the American Academy of Pediatrics expresses its sincere appreciation for the splendid cooperation and assistance of the Detroit Convention Bureau and Mr. Carl Sedan, the Executive Secretary, in the preliminary arrangements for and during the Annual Meeting of the Academy held at the Book-Cadillac Hotel, January 15 through 18, 1946.

Be it resolved, that the American Academy of Pediatrics expresses its sincere appreciation to the management of the Book-Cadillac Hotel for the splendid cooperation of all the hotel executives, as well as the employees and especially to Mr. George F. Ralston, Jr., Mr. Charles Loftis, Mr. Kurt M. Gebstadt, and Mr. John Gouci during the preparation for and the period of the Annual Meeting of the Academy, held January 15 through 18, 1946.

Be it resolved, that the American Academy of Pediatrics sincerely appreciates the courtesy of the Libby, McNeil and Libby Company, The Mennen Company, Mead Johnson and Company, and Harold H. Clapp, Inc., in providing the special events for members and their wives attending this meeting.

I move the acceptance of these resolutions.

(The motion was seconded and carried.)

THE PRESIDENT.—The report of the Nominating Committee by Dr. Joseph Henske is to be given by the Secretary.

THE SECRETARY.—The Nominating Committee has proposed Dr. Lee Forrest Hill for President-Elect and Dr. George F. Munns for Chairman of Region III.

(It was moved, seconded, and carried that the report of the Nominating Committee be accepted.)

THE PRESIDENT.—It is my great pleasure to induct into office Dr. Jay Durand as President of the Academy.

DR. DURAND.—I greatly appreciate the great honor the Academy has bestowed on me in selecting me as its president. In succeeding to this office I shall have difficulty in trying to follow such an outstanding president as we have had during the past year. I do not think I can fill his shoes, but fortunately I think I shall have to fill only one of those shoes because Dr. Wall has consented to continue to be a member of the Legislative Committee and look after the interests of the Academy in Washington. Without that assurance I would be very doubtful about carrying on in the next year in an efficient manner for the Academy.

(On motion duly made and seconded, the meeting adjourned sine die at 12:25 P.M.)

The Social Aspects of Medicine

SCATTERED IMPRESSIONS AND THOUGHTS OF A LISTENER AT THE ANNUAL SESSIONS

The first report of interest was the one by Dr. Sisson on Post-War Planning. Dr. Sisson gave an outline discussion of the program and was followed by several of his collaborators who dealt with special departments of the work. Dr. Sisson began by using a most extraordinary figure of speech: He said there had been suddenly thrust into his lap "a red-hot baby," a conception which might seem peculiar even to a most experienced cannibal. Dr. Sisson went on to state that the cost of this "red-hot baby" was to be \$8,000 a year according to original estimates, but that it had now risen to \$439,900 to cover a two-year period, and that both the United States Public Health Service and the Children's Bureau were making large contributions. While I was marveling at the expensiveness of this thermic prodigy, I heard Dr. Sisson confess that the true parent was Dr. John Hubbard and not himself, and that he had formally turned over the "baby" to Dr. Hubbard. The whole affair sounded mysterious and I wondered if the Academy, according to its confirmed habit, ought not to appoint another committee to investigate.

Dr. Sisson was followed finally by Dr. Hubbard himself. At the Academy dinner that evening I had the pleasure of sitting next Hubbard and inquired how soon he could finish the survey. He replied that he hoped to complete it within two years. I think that everyone felt that the survey was the only logical preliminary to the development of an adequate, wise plan for maternal and child health care, and that Dr. Hubbard was a most admirable choice to head it. I, for one, was troubled for fear that the work of the Committee would not be completed in time, since medical reform is threatening so rapidly. I hope that Hubbard can do the work in sampling fashion so that data will be available as a basis for action in case the need is suddenly forced. In reality the need for the information is "red-hot" now.

Dr. Wall's address was supposed to be the report of the Committee on Legislation but he explained at the very beginning that "to a certain extent" it reflected his own personal views. This seemed to me to be a most unfortunate error because, as the address proceeded, one was totally at a loss to know which were Dr. Wall's own particular opinions and which the views of the Committee. With that admission the "report" ceased to be a report. It can be said truthfully that the Committee did not make any report. Dr. Wall read the address from manuscript. It was written in highly literary form and contained figures of speech and quotations from the Bible and from Shakespeare. He went so far as to compare Senators Wagner and Murray and Representative Dingell to Shadrach, Meshach, and Abednego; and the Surgeon General of the United States Public Health Service, the Officials of the Children's Bureau, and the Federal Security Board to the witches in *Macbeth* peering into their boiling pot. The address was divided into a brief discussion of the Hill-Burton bill and more prolonged discussions of the Wagner-Murray-Dingell and Pepper bills. Dr. Wall expressed unqualified approval of the Hill-Burton bill, but made most scathing arraignments, full of irony, ridicule and innuendo, of the other two bills and including also the Children's Bureau. In making his points Dr. Wall went to great pains to cite specific passages and to support his statements with exact references. Obviously he had studied the legislation with great care and minuteness and from that point of view his address was a scholarly performance. In order to evaluate his criticisms, it is necessary to study them in detail with the bills in question before one. His points were often too detailed and involved to be immediately comprehensible. Many criticisms were on very small matters. Dr. Wall's accusations against the Children's Bureau (they were really insinuations) revolved around the promise of the Children's Bureau

not to continue the EMIC program (Dr. Wall suspected that the Pepper bill was merely the EMIC program disguised in new clothes) and in its failure to consult accredited Academy representatives. He closed with the quotation from the Bible, Mark 4:25: "For he that hath, to him shall be given; and he that hath not, from him shall be taken even that which he hath," saying that he had never been able to understand it until the impending bills came along, a statement difficult to take literally.

If I had been a stranger who had happened into the room by accident, I would have gained the impression from Dr. Wall that the Pepper bill was a mass of defects and did not possess a solitary virtue. Just the force of Dr. Wall's enumeration made one conclude that it had many weaknesses. But were they beyond correction? Did the bill have no redeeming qualities? I gained no idea. I should have inferred also that the Children's Bureau was a slippery organization, ambitious for power, conspiring to get control of the medical care of children and to take away the practice of Pediatrics from the Pediatricians.

When Dr. Wall concluded, he was greeted with loud, sustained applause. Evidently his address was much admired and enjoyed. At the witty passes I could see Dr. Arnold Gesell, who sat just in front of me, shaking all over with laughter, including his shoulders. However, when one considers what should have been its object, the address had serious defects. First, as already pointed out, it was so composed that no one could differentiate what was Wall and what Committee. Herein it lost much of its force. How the Committee ever allowed Dr. Wall to report himself instead of them, I cannot imagine. Second, one expected a judicial statement with good and bad pointed out, estimated and weighed against each other. Instead, the address was a summing up oration of a prosecuting criminal lawyer. I walked out of the room with Harold Root of Waterbury who, I know, does not like the Pepper bill. He turned to me with the remark, "It can't be as bad as all that." The literary furbishings all tended to make one regard the address as an ornamental piece rather than a practical utensil and its ironical insinuating tone could not help but make one feel that there might exist prejudice. Third, it was bare of anything constructive. These were the reasons, I think, why the Academy turned away from it in favor of the more constructive criticism of Butler, delivered from the floor, for their final recommendations.

I cannot allow Dr. Wall to escape the consequences of one of his figures. He compared Senators Wagner and Murray, and Representative Dingell to Shadrach, Meshach and Abednego. His words were: "This latest legislative proposal emanating from the triumvirate of Shadrach, Meshach and Abednego, reappeared on the scene from their fiery furnace where medicosocial legislation is welded. . . ." If one will turn to the book of Daniel, Chapter 3, he will find the story concerning these three men. Nebuchadnezzar made an image of gold. At the dedication he commanded that at the "sound of the cornet, flute, harp, sackbut, psalter, dulcimer, and all kinds of musick," all should fall down and worship the golden image, Shadrach, Meshach, and Abednego declined. Therefore Nebuchadnezzar had the fiery furnace made seven times hotter than ever before and commanded that Shadrach, Meshach, and Abednego be thrown into it. In its quaint language the Bible states: "Then these men were bound in their coats, their hosen, and their hats and their other garments, and were cast into the midst of the burning fiery furnace." The heat was so great that it slew those who threw them in. When Nebuchadnezzar, a little later, looked into the furnace, he saw not three men walking around, but four and recognized at once that "the form of the fourth is like the Son of God." Nebuchadnezzar, therefore, came to the mouth of the burning fiery furnace and called Shadrach, Meshach, and Abednego to come out, addressing them as "ye servants of the most high God." On examining their bodies it was found that "the fire had no power, nor was an hair of their head singed, neither were their coats changed, nor the smell of fire had passed on them." Correctly interpreting the miracle, Nebuchadnezzar reversed himself immediately and completely, exclaiming, "Blessed be the God of Shadrach, Meshach, and Abednego, who hath sent his angel, and delivered his servants that trusted in him, and have changed the king's word, and yielded their bodies, that they might not serve nor worship any god, except their own God." Nebuchadnezzar then issued a new decree. "That every people, nation and language, which speak any thing amiss against the God of Shadrach, Meshach, and Abednego, shall be cut in pieces, and their houses shall be made a dunghill: because there

is no other God that can deliver after this sort.' Then the king promoted Shadrach, Meshach, and Abednego in the province of Babylon. You see, Dr. Wall allied himself with the wrong side against the right side. He is now confronted logically with alternatives: Either like Nebuchadnezzar he must shift over and must now support the Wagner-Murray-Dingell bill or else he must submit to being cut in pieces and his house being made a dunghill.

Unfortunately I was called out and missed all but the last part of Dr. Sinai's paper. But that alone indicated a most scholarly presentation.

With great courtesy and thoughtfulness, Dr. Wall descended from the platform and asked Dr. Butler to speak. Dr. Butler was on crutches because of a broken leg from skiing.

I shall not make any attempt to outline Dr. Butler's remarks other than to say that he pointed out that the bill did have a good side. He then stated that he himself did not approve of the Pepper bill in its present form and offered thirteen specific criticisms. The criticisms differed from Dr. Wall's in the respect that they indicated not only where the bill was defective, but also how it could be remedied. He maintained that the Academy could not afford to ignore the Pepper bill or to disapprove it without recording its specific reasons.

Stanley Nichols, who has done much for children and has stood with strength and tact for what he thought right in the politics of his own bailiwick, advocated as the best procedure to attempt to bring together all interested groups, organized medicine, pediatrics, nursing, government organizations, organized labor, and so forth, in a grand effort to develop a scheme of medical care agreeable to all. He had been kind enough to have me to dinner the night before and had spent some time telling me his views. I think that when he spoke, he hoped I would second his proposal, and I must confess that I wished for the sake of so fine a man I could do so. But I did not believe that at the present time anything would result beyond disagreement and deadlock. Reverting to Dr. Wall's figure of the witches, I think the situation must stew some more before a solution can be obtained in that way. Proposed social legislation, such as that which confronts us, the strikes and social upheavals all around us, are making all groups think and advance, and even leaders of the American Medical Association, like Fishbein, have moved a long way from the position they occupied at the time the Government brought suit against them for preventing the development of the Group Health Association in Washington, D. C.

Grulee created a surprise at the business session. He rose from his seat on the platform and announced that, although he had not thought as much as he should about the matter which he was going to present, he had not been able to sleep well for several nights on account of it. I was perplexed by this introductory remark with its obvious contradiction and was not sure what it meant at the time or afterward. The next moment he revealed his trouble; it was the same as that which Wall had disclosed in his speech of the morning. But Grulee went further than Wall to the point of suggesting, what I took to be a feeler, that he might later even be in favor of severing the Academy's support from the Children's Bureau altogether. Obviously many present approved of what Grulee said, for there was considerable applause.

The accusations or insinuations that the Pepper bill is the EMIC Program disguised and that the Children's Bureau deliberately worked a deception on the Academy are in my opinion unjust, and to hear them expressed by men of such prominence in Academy affairs was to me personally disquieting and even painful. The Children's Bureau has been a tremendous power for good in the country. No one can dispute this statement. I wish only that all other government agencies were as free from taint and directed on the same elevated plane. Much of the adverse criticism which the Bureau has received it has brought on itself by insisting on standards so high as to impose annoying and even exasperating difficulties on those carrying out its projects. If I were to wish something different in the Children's Bureau, it would be that it operated with less rigidity. But no one can impugn its high motives. I do not believe that any levelheaded member present thought for one moment of cutting loose from the Children's Bureau. Both Academy and Bureau would be greatly weakened by the separation, the Academy even more than the Bureau, for the Academy would be shorn of its great instrument of effectiveness. It is through the Children's Bureau that the Academy, when it does develop its program, can reach the country and put its ideas into execution.

The Pepper bill is not any new conception. In general plan it was already embodied in the Wagner-Murray-Dingell bills, but in its present form as a separate document the plan has been worked out and elaborated in much more detail. The central idea of getting good medical care to all mothers during the child producing and nurturing periods and to all children is just a part of the widely entertained conception of bringing adequate medical care within the reach of everybody. Really the Wagner-Murray-Dingell bills, the British Beveridge Plan, and the British White Paper are all similar in their design and aims, as a result of similarity in present-day thinking in this country and abroad, and the Pepper bill is just a fragment from this mosaic. It is really wrong to consider these proposed health legislations as the products of the minds of certain individuals, as the theory of evolution was the product of Darwin's mind, or relativity, Einstein's. Rather, they represent in concrete form the collective desires, the longings, the unfulfilled wishes, if you like, of great numbers of people, for security in regard to medical care just as for financial security. The authors of these bills, Senators Wagner, Murray, and Pepper and Representative Dingell, are the ones who possessed the social interest and the wit to perceive how general those hopes were and that the time had arrived when it might be possible to obtain realization of them by legislation. If Senator Pepper had not produced the bill which goes by his name, someone else would have done so promptly.

If Senator Pepper came to the Children's Bureau for aid on developing his bill, was the Children's Bureau bound to refuse because it had announced it would not continue the EMIC programs after the war? The EMIC program was for the wives and children of servicemen. Is the Children's Bureau bound by its statement, that it would not continue aid to the families of servicemen, never to participate in any plan to place medical care for children at the doors of all who need it? The stated aim of the Academy as quoted from the resolution adopted in 1944 is: "To make available to all mothers and children in the United States of America all essential preventive, diagnostic and curative medical services of high quality, which used in cooperation with the other services for children will make the country an ideal place for children to grow into responsible citizens." Is the Children's Bureau forbidden to participate in anything like this? If the Academy develops a nation-wide program of its own, will the Children's Bureau be prevented from sharing because of its agreement not to renew the EMIC program? In our relations with the Children's Bureau does no fault rest with us? The Children's Bureau would rather cooperate with the Academy than with any other organization. But what constructive program has the Academy ever offered in which the Children's Bureau could cooperate, save the study of the Committee on Post-War Planning, toward which the Bureau is contributing through service of its staff the equivalent of \$25,900. If Grulee, instead of accusing the Children's Bureau, had pointed this out and had called for more constructive leadership, in my judgment his words would have been more serviceable. When a storm suddenly destroyed the pontoon bridge which Xerxes had had constructed across the Hellespont in his invasion of Greece, he ordered the heads of his chief engineers cut off, the water scourged and fetters thrown into it. The talk against the Children's Bureau just discussed seems to me to savour somewhat of Xerxes' thinking.

Grulee's speech brought Butler and later Helmholtz to their feet in defense of the Bureau, but I shall not go into that worn-out controversy. Butler, however, in the course of his discussion, explained something which interested me very much. It was that, according to the technique of procedure in Congress, a bill is drawn up and proposed, not as a final, but rather as a trial document calculated to draw criticism and become a basis for its reconstruction and change. The Pepper bill, Butler stated, should not be considered "the final form of a bill which is to be thrust upon us." This viewpoint is of importance to us because it suggests that the Pepper bill can perhaps be remodeled into a form acceptable to the Academy. The resolution of the Executive Committee, passed at this Detroit meeting, places the Academy on record as favoring Federal aid to those unable to pay for medical services and the general aims of the Academy, as defined in the splendid resolution, already quoted, passed at the St. Louis meeting, and the general aims of the Pepper bill are identical. The fundamental points of disagreement are in methods of administration.

In the course of this discussion the comment was made by Butler that all the members of the Committee on Legislation were over 60 years of age. I am 68 years old and so can say, without danger of injury to feelings, what everyone knows, that men beyond 60 are likely to be poor leaders into new fields. Some of us are mentally so fixed as to be unable to change; some have become too nearsighted to see the superiority of new ideas; some are so timid as to fear anything which differs from past experience; some are so satisfied with the past that they can never look out through any other window; some, not being able to keep up with progress, try to hold it back; some have none of these characteristics; most of us have some of them. I hope very much that the Academy will bring youth into its leadership as soon as possible. I should like to see the young men freshly returned from the war in positions of influence because they have had the opportunity to live through new experiences and to see life and their pasts from new angles. Some years ago The Society for Clinical Investigation voted to make all members over 45 years emeritus. I was 46 at the time and remember hearing a voice behind me say: "Now for the slaughter of the swine." I was too self-conscious to look around to see the owner of the voice, but it is a comfort for me now to think that with the passage of years Circe has him, too, grunting in her pen. But the move strengthened the Society enormously. I am not advocating an age limit for Academy membership, though it might be a good plan to impose one on officers, but rather that youth be accorded its rightful influence in Academy affairs.

Dr. Wall's presidential address was a very nice, simple, straightforward summary of the accomplishment of the Academy during his year of office.

I think that everybody approved of the resolution adopted by the Executive Board with the exception that it contained no recommendation of a specific constructive nature. Dr. Roger Kennedy pointed out this deficiency and proposed that the Academy add to the resolution its objection to the Pepper bill on the basis of the thirteen points of criticism introduced by Butler which were to be included. This was noted affirmatively. I should assume from the action of the Academy that the Academy would approve of the Pepper bill, if it could be corrected to the satisfaction of the members at the points where the thirteen objections were made.

In conclusion, I make two observations: The first is to point out how splendid the discussion was. Even discussion which went off on useless side paths seemed to serve to make clearer the one which the Academy ought to follow. As the final morning wore on I think that all felt a much clearer grasp of the problems at issue. The second is to comment on the prowess of Dr. Allan Butler, who undoubtedly carried off the honors. Whether one agreed with him or not, one had to admit that he seemed to have remarkable grasp of all matters under consideration and that he showed the ability for clear thinking and clear statement which filled many of us with envy. His was the dominating mind at the meeting. Witnessing him in action, one felt sure that the spiral fracture of the fibula did not have its counterpart in his brain.

E. A. P.

News and Notes

The following were certified by the American Board of Pediatrics at the examination held in Atlantic City in December, 1945.

- Dr. Charles Abler, 55 E. 174th Street, Bronx 52, N. Y.
- Dr. George Roland Alpert, 211 West 106th Street, New York 25, N. Y.
- Dr. Katherine H. Anderson, 415 North Spring Street, Winston-Salem, N. C.
- Dr. Marguerite E. Bagge, 636 Church Street, Evanston, Ill.
- Dr. John Donald Bailey, 607 Eighth Street, Rapid City, S. D.
- Dr. John B. Bartram, Green and Coulter Streets, Philadelphia, Pa.
- Captain Ralph Edmond Baxter, Medical Corps, Army Air Forces Convalescent and Regional Hospital, Coral Gables, Fla.
- Dr. George Bialkin, Children's Clinic, 2649 Proctor Street, Port Arthur, Texas
- Dr. Emanuel B. Brandes, 4715½ Fannin Street, Houston, Texas
- Dr. Amy Breyer, 436 Capitol Avenue, Hartford, Conn.
- Dr. John P. Burgess, 2411 North Thirty-Eighth Street, Rock Island, Ill.
- Dr. Philip S. Chasin, 11-39 Seventy-sixth Road, Forest Hills, N. Y.
- Dr. Joan Neilson Daly, 108-19, Seventieth Road, Forest Hills, N. Y.
- Dr. William W. Davis, Oak Hill, W. Va.
- Dr. Charles P. DeFuccio, 12 Duncan Avenue, Jersey City, N. J.
- Dr. Joseph Henry Di Leo, 175 East Sixty-Eighth Street, New York, N. Y.
- Dr. Herman Eisenberg, 701 Kay Street, N. E., Washington 2, D. C.
- Dr. Thomas Campbell Goodwin, 16 East Biddle Street, Baltimore, Md.
- Dr. Werner Karl Gottstein, 2376 East Seventy-First Street, Chicago 49, Ill.
- Dr. Lester J. Greenberg, 1167 Virginia Street, Far Rockaway, N. Y.
- Dr. Paul Hogg, Thirty-First Street and West Avenue, Newport News, Va.
- Dr. Hedwig Heda Holzer, 591 Morton Street, Dorchester, Mass.
- Dr. Ruth M. Kraft, 1077 Fisher Building, Detroit 2, Mich.
- Captain Philip J. Kresky, 1300 South Covell Avenue, Sioux Falls, S. D. (formerly Brooklyn N. Y.)
- Dr. Harvey Deppen Leinbach, Jr., 1101 Evergreen Road, Reading, Pa.
- Dr. Audrey Jane McDonald, 814 Medical Arts Building, Ft. Worth, Texas
- Dr. Israel Miller, 1014 Lenox Road, Brooklyn, N. Y.
- Dr. J. Leonard Moore, 107 Library Place, Princeton, N. J. (formerly Beirut, Syria)
- Dr. Charles Anthony Murphy, 141 Wheller Avenue, Cranston, R. I. (formerly Stamford, Conn.)
- Dr. James Joseph Quilligan, Jr., 1313 East Ann Street, Ann Arbor, Mich.
- Dr. Helen Seibert Beardon, University Hospital, Ann Arbor, Mich.
- Captain Edward T. Reilly, Medical Corps, 1452nd Army Air Forces Base Unit, Air Transport Command, APO 462, c/o Postmaster, Minneapolis, Minn. (formerly Brooklyn, N. Y.)
- Dr. Dean Winn Roberts, 2411 North Charles Street, Baltimore, Md.
- Dr. Laura Ross-Venning, 1620 Queens Road, Charlotte 4, N. C.
- Dr. Robert Thornton Rutherford, Jr., 207 Doniphan Building, Alexandria, Va.
- Dr. Alec Robert Schwartz, 5801 Beacon Street, Pittsburgh, Pa.
- Captain Aaron Schwinger, Medical Corps, Station Hospital, Stewart Field, Newburgh, N. Y.
- Dr. Walter F. Sethuey, 1016 Sheridan Road, Menominee, Mich.
- Dr. Christopher Harrison Snyder, 3975 Broadway, New York, N. Y.

Dr. Eleanor Robb Stein, 1516 North Second Street, Harrisburg, Pa.

Dr. Robert Hosea Trimby, 122 West Hillsdale, Lansing 15, Mich.

Dr. David William Van Gelder, 500 Reymond Building, Baton Rouge, La.

Dr. William Lucas Venning, 1620 Queens Road, Charlotte 4, N. C.

Dr. Helen Margaret Wallace, 125 Worth Street, New York, N. Y.

Captain Theresa Ting Woo, Medical Corps, Strong Residence, 1011 Seventeenth Street, N. W., Washington, D. C.

Dr. Benjamin J. Wood, 5432 Bartlett Street, Pittsburgh 17, Pa.

Dr. Paul V. Woolley, Jr., 3181 Southwest Marquam Hill Road, Portland, Ore.

Dr. Ella Zuschlag, The Mayo Clinic, Rochester, Minn.

PRECEPTORSHIPS

It has come to the attention of the American Board of Pediatrics from several sources that an erroneous impression is being passed around regarding preceptorships. Preceptorships *will not* be acceptable as preliminary pediatric training, but may be used as refresher work and accredited time in practice by those who have completed their preliminary training.

The publication of a new abstract journal for pediatrics, *The Quarterly Review of Pediatrics*, under the editorship of Dr. Irving J. Wolman of Philadelphia, has been announced by the publishers, The Washington Institute of Medicine. The journal will appear every four months beginning with the first issue in February, 1946.

Joe W. Savage of Charleston, W. Va., has been appointed executive director of the National Foundation for Infantile Paralysis.

Dr. Chester A. Stewart, Professor of Pediatrics and Director, Department of Pediatrics, Louisiana State University School of Medicine, New Orleans, La., died Feb. 8, 1946.

The Pediatrician and the War

Major J. Lewis Blanton of Fairmont, West Virginia, has been promoted to Lieutenant Colonel in the Army.

The following have been released from service:

Dr. Robert H. Detwiler, Arlington, Va.

Dr. Leon De Vel, Grand Rapids, Mich.

Dr. C. Barton Etter, Memphis, Tenn.

Dr. Martin A. Quirk, Red Bank, N. J.

Dr. Alvin C. Rambar, Chicago, Ill.

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Original Communications

ISOLATION OF ST. LOUIS ENCEPHALITIS VIRUS FROM THE PERIPHERAL BLOOD OF A HUMAN SUBJECT

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ST. LOUIS, MO.

IN SO far as we are aware, viremia in St. Louis encephalitis has not been demonstrated in the human subject. Under experimental conditions in animals, however, viremia with the virus of St. Louis encephalitis has been demonstrated by a number of investigators. Webster and Clow¹ and Webster² were able to show that the St. Louis virus could be recovered from the blood of mice almost immediately following subcutaneous inoculation and for twenty-four hours thereafter. After intracerebral inoculation the virus was present in small amounts in the blood immediately following injection and again just prior to death. Hammon and associates³ have shown that the St. Louis virus is present in the blood of horses from twenty-four to forty-eight hours after subcutaneous inoculation. In connection with a study of the experimental transmission of St. Louis encephalitis virus by mosquitoes, Hammon and Reeves⁴ demonstrated viremia in chickens and ducks forty-eight hours after inoculation by subcutaneous route and from twenty-four to forty-eight hours after being bitten by experimentally infected mosquitoes. In the Syrian hamster, Blattner and Heys⁵ have shown that the virus of St. Louis encephalitis is present in the blood from eight to seventy-two hours following intraperitoneal inoculation.

In the case of certain other neurotropic viruses recovery from the blood has been accomplished in human patients as well as in experimental animals. By inoculation of mice, Japanese B virus was isolated from the blood and spinal fluid of a human patient in early stage of infection.⁶ Howitt⁷ recovered the virus of Western equine encephalomyelitis from stored blood serum taken from an adult whose illness had been diagnosed as encephalomyelitis. Studies of this strain of virus^{8, 9} in experimental animals, including the horse, demonstrated that the virus is recoverable during the febrile period from both cardiac and peripheral blood, whole blood and serum. Virus was no longer recovered from the blood after defervescence. Howitt¹⁰ showed that the virus of Western equine was present in the blood from eight to thirty-three hours following nasal

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instillation in the guinea pig. More recently Gwatkin and Moynihan¹¹ reported the isolation of Western equine virus from spinal fluid taken ten days after onset of symptoms in a human patient. In Russian encephalitis the virus has been recovered occasionally from the spinal fluid of human patients but is more readily recoverable from the blood.^{12, 13}

The virus of lymphocytic choriomeningitis has been recovered with comparative ease from both the spinal fluid and the blood of human patients.¹⁴⁻¹⁶ Experimental inoculation of human volunteers¹⁷ revealed that viremia begins shortly before onset of fever and persists for twelve to fourteen days.

From the spinal fluid of a patient whose symptoms and signs were suggestive of encephalitis, Armstrong¹⁸ isolated a virus which was identified as a strain of herpes simplex.

On the basis of such observations it seems likely that viremia does occur in the human patient with encephalitis, but that in many instances the virus is no longer present in the blood stream by the time that symptoms and signs of central nervous system involvement appear. Despite these theoretical considerations, it has seemed worth while to attempt the isolation of virus from the blood stream in this type of patient, and numerous attempts have been made at the St. Louis Children's Hospital to recover virus from blood and spinal fluid of patients with clinical encephalitis.

On July 6, 1945, an 8-year-old boy, resident at Wood River, Ill., twenty miles distant from St. Louis, was admitted on the service of Dr. Alexis F. Hartmann with the following history: During the four days prior to admission, according to the mother, he became extremely drowsy, sleeping all day, rousing intermittently to ask for water. He would fall asleep again almost immediately. Two days before admission, he seemed somewhat improved but had fever and appeared listless. The day before admission he became worse; the temperature rose to 38.9° C., and vomiting was severe. On admission the patient appeared ill and was moderately dehydrated, but the only definite finding was mild pharyngitis. The temperature at the time of admission was 38.2° C. During the course of the examination the boy complained constantly of severe headache. On the way to the admitting ward he seemed disoriented and persisted in sitting in one corner of the elevator. As he was a well-adjusted child, the parents considered this behavior very unusual.

Considering the possibility that this child might have encephalitis, lumbar puncture was advised. The spinal fluid obtained was slightly opalescent and contained 250 lymphocytes. The Pandy was slightly positive. Immediately following lumbar puncture, blood was taken from the antecubital vein, using sterile precautions. Some of the specimen was added to a tube containing the sodium salt of heparin (Lederle), 0.01 ml. to 10 ml. of whole blood; another portion of the blood sample was saved for serum; and a third portion was set aside for antibody study.

After dehydration was corrected, the patient showed marked improvement. Subsequent course in the hospital was unusually mild. At no time were definite meningeal signs noted. Laboratory data revealed the following: Urinalysis, negative; white blood cells, 6,300 with 2 eosinophiles, 8 stabs, 31 segmented cells, 55 lymphocytes, and 4 monocytes. Tuberculin test was negative. The spinal fluid sugar was 81.5 mg. per cent, and simultaneous blood sugar was 95.5 mg. per cent. Lumbar puncture repeated three days after admission showed the presence of 365 cells, 42 per cent of which were lymphocytes. Seven days after admission the lumbar puncture showed 41 cells, all of which were lymphocytes. The patient was discharged in excellent condition on the tenth hospital day. There was no evidence of sequelae.

EXPERIMENTAL FINDINGS

Immediately after lumbar puncture the spinal fluid was inoculated onto the chorioallantoic membrane of four embryonated hen's eggs: two eggs of seven days' incubation; two eggs of twelve days' incubation. There was no evidence of growth on these membranes. After ninety-six hours the chorioallantoic membranes of these four eggs were removed, pooled, and passed to four adult white Swiss mice, 0.03 ml. intracerebrally and 0.1 ml. intraperitoneally. These mice remained free of signs during three weeks of close observation. Four 9-day-old white Swiss mice were injected with the original spinal fluid: 0.03 ml. intracerebrally and 0.1 ml. intraperitoneally. None of these mice developed signs of illness.

Within five minutes after obtaining the blood sample, heparinized blood was inoculated into six littermates of the 9-day-old mice used for the spinal fluid test, 0.05 ml. of heparinized blood being injected intraperitoneally into each of the six 9-day-old mice. Simultaneously, heparinized blood was injected into four young adult white Swiss mice, 0.1 ml. intraperitoneally, 0.03 ml. intracerebrally. Serum separated from the clotted blood was injected into six young white Swiss mice, 0.03 ml. intracerebrally and 0.1 ml. intraperitoneally. Some of this serum was also injected into eggs: two of seven days' incubation and two of twelve days' incubation. There was no evidence of virus growth on the chorioallantoic membranes. Of the inoculated mice none showed signs of illness except the six 9-day-old mice which had been injected intraperitoneally with heparinized blood.

On the seventh day after inoculation these six mice appeared listless. Within two hours five of them were dead. The one remaining alive was in convulsions. The brain, spleen, and lungs of each of the five were removed, frozen, and stored in a refrigeration unit* maintaining a temperature of -56° C. A small piece of tissue from each organ was cultured in tryptose-phosphate broth. None of these cultures showed bacterial growth. Likewise, the brain, spleen, and lungs were removed from the one mouse remaining alive. Bacterial cultures of tissue in broth remained sterile. The spleen and lungs were frozen and stored. The brain was emulsified in tryptose-phosphate broth and the resulting supernatant fluid inoculated intracerebrally, 0.03 ml., into four young adult mice. Blood agar culture of the inoculum gave no growth. On the ninth day following injection, two of these young adult mice showed signs of illness with convulsive movements. The brain of each was removed, cultured, and passed to four adult mice. Three to five days following this inoculation two of the eight mice were dead; three were in convulsions. The brains from this passage were cultured and passed to other adult Swiss mice. Again within three days definite convulsions were noted. At the present writing the newly isolated virus has been well established in white Swiss mice (ninth passage) and produces convulsions and death in two to three days after inoculation of 0.03 ml. intracerebrally, 10^{-1} suspension. In all passages cultures of blood, brain, spleen, and lung were negative.

*This refrigeration unit was purchased from funds made available by the Children's Research Foundation of St. Louis.

The newly isolated strain of virus is filter-passing: Berkefeld N and V-fine filters. At the second intracerebral mouse passage the virus kills adult white Swiss mice through the 10^{-6} dilution; at the seventh intracerebral passage, the virus kills adult white Swiss mice through the 10^{-8} dilution.

Microscopic sections of mouse brains from the second and the sixth intracerebral passages show an encephalitic process which is apparently indistinguishable from that produced in the mouse by a known strain (Hubbard) of St. Louis encephalitis virus.

The newly isolated virus was inoculated onto the chorioallantoic membrane of the developing hen's egg. Within four to five days definite evidence of virus growth was noted. Passage of egg membrane to mice produced convulsions in three to four days. The newly isolated virus was injected also into a rabbit, 0.06 ml. 10^{-1} suspension intracerebrally. No evidence of illness has been noted. One adult guinea pig was inoculated, 0.1 ml., 10^{-1} , intraperitoneally, and 0.1 ml. 10^{-1} sublingually. A second adult guinea pig received 0.25 ml. of 10^{-1} suspension intraperitoneally. A young guinea pig, approximately 3 weeks of age, was injected with 0.25 ml. of 10^{-1} suspension intraperitoneally. Its littermate received 0.04 ml., 10^{-1} , intracerebrally. Cultures of all inocula were bacterially sterile. There has been no sign of illness in any of these guinea pigs.

Using the newly isolated strain of virus, parallel serum-virus neutralization tests were performed with blood serums obtained from the patient during clinical course and with sera of rabbits immunized against St. Louis encephalitis virus, Hubbard strain, lymphocytic choriomeningitis, and herpes simplex. Controls consisted of mixtures with broth alone and with normal human serum. It will be seen from the results of this test, which are given in Table I, that during

TABLE I. SERUM-VIRUS NEUTRALIZATION TESTS USING NEWLY ISOLATED VIRUS SHOWING INCREASING TITER OF ANTIBODY IN PATIENT'S SERUMS; NEUTRALIZATION OF VIRUS BY ST. LOUIS IMMUNE RABBIT SERUM, LACK OF NEUTRALIZATION BY LYMPHOCYTIC CHORIOMENINGITIS AND HERPES RABBIT SERA*

DILUTIONS OF VIRUS	PATIENT'S SERUM I 4 DAYS AFTER ONSET	PATIENT'S SERUM II 9 DAYS AFTER ONSET	PATIENT'S SERUM IV 28 DAYS AFTER ONSET	IMMUNE RABBIT SERUM LYMPHOCYTIC CHORIOMENINGITIS	IMMUNE RABBIT SERUM ST. LOUIS (HUBBARD)	IMMUNE RABBIT SERUM HERPES (H. F.)	NORMAL HUMAN SERUM	CONTROL BROTH
10^{-2}	3 3 3 3	3 3 3 3	S S S S	3 3 3 3	3 3 3 3	3 3 3 3	T 3 3 3	3 3 3 3
10^{-3}	3 3 3 4	S S S S	T S S S	3 3 3 3	3 3 3 3	3 3 3 3	3 3 3 3	3 3 3 3
10^{-4}	3 3 3 3	S S S S	S S S S	3 3 3 3	3 3 3 3	3 3 3 3	3 3 3 3	3 3 3 3
10^{-5}	S S S S	S S S S	S S S S	3 3 3 3	3 3 3 3	3 3 3 3	3 3 3 3	3 3 3 3

*Each figure represents one mouse; figure indicates day of convulsions and death; S = survived; T = died trauma.

the clinical course the patient developed increasing titer of humoral antibody to the newly isolated virus. As is shown also in Table I the virus is not neutralized by lymphocytic choriomeningitis or herpes immune rabbit sera but is neutralized completely by St. Louis encephalitis immune rabbit serum. Another parallel protection test was carried out using the newly isolated strain

TABLE II. SHOWING COMPARABLE INCREASE IN TITER OF ANTIBODY TO THE NEWLY ISOLATED VIRUS ("M" STRAIN) AND TO A KNOWN STRAIN OF ST. LOUIS ENCEPHALITIS VIRUS (HUBBARD)*

DILUTIONS OF VIRUS	PATIENT'S SERUM I 4 DAYS AFTER ONSET	PATIENT'S SERUM IV 28 DAYS AFTER ONSET	NORMAL HUMAN SERUM	IMMUNE RABBIT SERUM ST. LOUIS ENCEPHALITIS	CONTROL BROTH
<i>"M" Strain of Virus</i>					
10-3	3334	SSSS	3334	SSSS	3333
10-4	3444	SSSS	3334	SSSS	3334
10-5	444S	SSSS	4444	SSSS	4444
<i>St. Louis Encephalitis (Hubbard Strain)</i>					
10-3	3344	SSSS	3333	SSSS	3334
10-4	4445	SSSS	3333	SSSS	4444
10-5	SSSS	SSSS	3444	SSSS	4445

*Each figure represents one mouse; figure indicates day of convulsions and death; S = survived.

and a known St. Louis encephalitis strain of virus (Hubbard). The results summarized in Table II show that during his clinical recovery, the patient developed a comparable increase in titer of antibody to the newly isolated strain and to the known St. Louis virus.

Certain aspects of this study are worthy of note. The unusually mild clinical course of this illness, shown to be due to a neurotropic virus, lends support to the contention that many such cases may occur without accurate etiologic diagnosis. Persistence of the virus in the peripheral blood approximately four days after onset of clinical symptoms is considered unusual. It is a matter of conjecture whether any relationship exists between the prolonged viremia and the paucity of central nervous system manifestations in this patient.

SUMMARY

A filtrable virus has been isolated from the blood of a patient whose clinical manifestations were suggestive of a virus infection with minimal central nervous system involvement. The infectious agent isolated is neutralized by serum of a rabbit immunized to a known strain (Hubbard) of St. Louis encephalitis virus. During the clinical course the patient developed increasing antibody titer to the newly isolated virus and to known St. Louis encephalitis virus (Hubbard).

Two criteria for the diagnosis of a virus disease have been satisfied; namely, isolation of an infectious agent from the patient, and development during the course of clinical illness of type-specific humoral antibodies.

This work represents the first instance of the isolation of the St. Louis encephalitis virus from a human subject during life. It is the fourth instance in which the St. Louis virus has been isolated from natural sources, the first being the initial isolation from human brain tissue taken at autopsy,^{19, 20} the second from mosquitoes collected in nature during an epidemic,²¹ the third from the bodies of chicken mites collected in nature during a nonepidemic period.²²

The intraperitoneal injection of young mice with relatively large inocula may prove to be generally applicable for the isolation of virus, especially for the detection of small amounts.

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FURTHER OBSERVATIONS OF EPIDEMIC DIARRHEA OF THE NEWBORN

I. OBSERVATION OF A BIPHASIC TYPE OF CLINICAL COURSE

II. THERAPEUTIC MEASURES INCLUDING PROPHYLACTIC AND THERAPEUTIC USE OF GAMMA GLOBULIN*

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IN A previous outbreak¹ a group of patients with epidemic diarrhea of the newborn responded remarkably well to a regimen of treatment in which particular attention was directed to the correction of states of acidosis and to the maintenance of fluid balance. Although the infants affected in a subsequent outbreak of the disease were treated according to the same principles, less favorable results were obtained. Some of the infants had a unique course characterized by relapses which frequently terminated in death.

EPIDEMIOLOGY

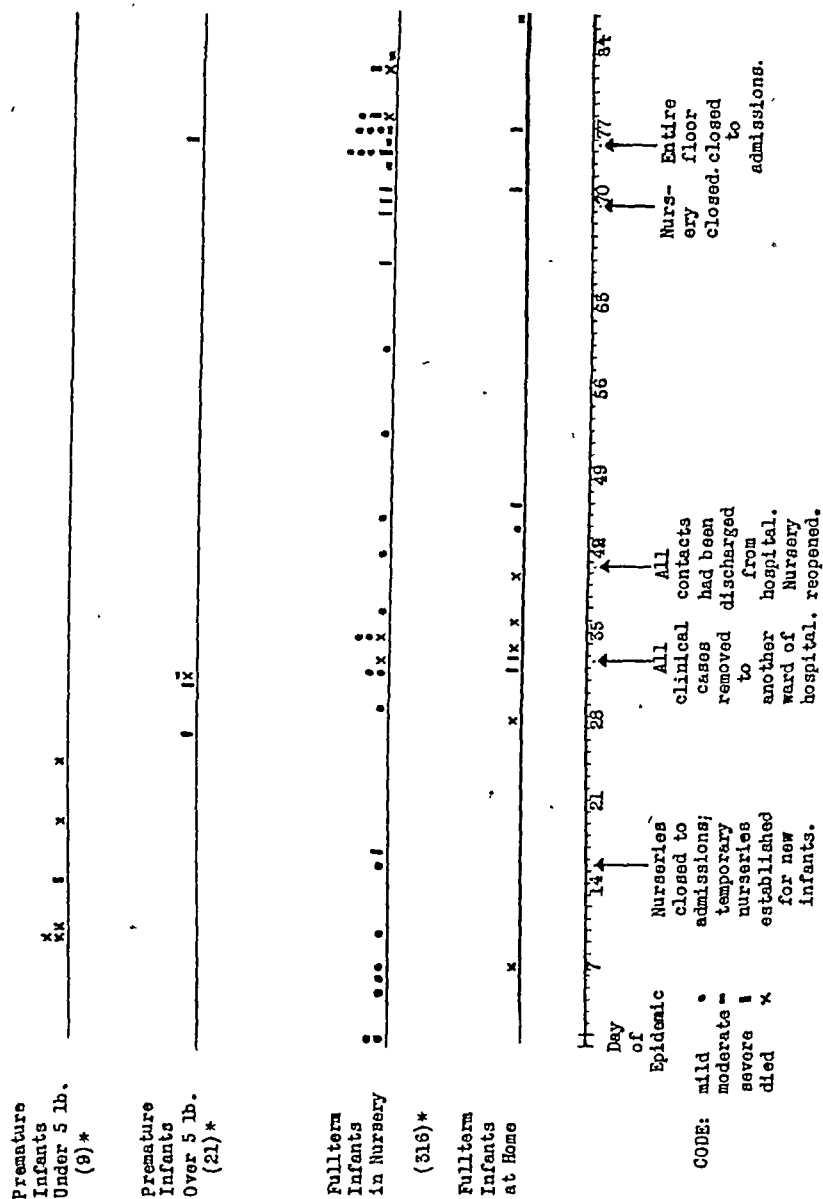
The difficulty of establishing the diagnosis of initial cases of epidemic diarrhea of the newborn was encountered in this outbreak. One infant in each of two nurseries for full-term infants in the Temple University Hospital developed loose stools early in September, 1944. One of them, who had lost considerable weight, was isolated from the other infants, but his subsequent course was uneventful and he was discharged from the hospital on the following day. The other infant, who showed no other evidence of illness, was not isolated until the second day of mild diarrhea, when he had a moderate loss of weight. His subsequent course was also uneventful, the character of his stools improving with modification of the feeding. At the time, therefore, the loose stools of these patients were considered of noninfectious nature, but in retrospect it seems probable that they were the manifestations of the initial mild cases of epidemic diarrhea of the newborn. On successive days other infants in one of these nurseries developed loose stools, and an infant who had been discharged apparently in satisfactory condition one day previously was readmitted to the hospital after the development of diarrhea, vomiting, and loss of weight. The clinical picture of this infant was not typical of epidemic diarrhea of the newborn but resembled that of other infants who had been admitted to the hospital about the same time but who had not had any previous contact with the nursery. Nine days after the first two instances of mild diarrhea, two infants in the premature nursery developed loose stools, on the following day a third infant was similarly affected, and within a short time three other in-

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*The name gamma globulin is used for purposes of abbreviation to describe concentrated normal human serum gamma globulin (immune serum globulin) prepared by the methods of plasma fractionation (Cohn, E. J., Oncley, J. L., Strong, L. E., Hughes, W. L., Jr., and Armstrong, S. H., Jr.: J. Clin. Investigation 23: 417, 1944).

infants in that unit developed the disease. The premature nursery was a separate unit, and there was a separate nursing personnel for it. It was recognized that these infants probably had epidemic diarrhea of the newborn and that in each of the three nurseries others had been inadvertently exposed to the disease.

CHART I. DEVELOPMENT OF CLINICAL CASES IN AN EPIDEMIC OF DIARRHEA OF THE NEWBORN



* Total number of infants exposed to disease.

Clinical cases subsequently developed in both of the nurseries for full-term infants and among the infants who had been dismissed recently from the hospital (Chart I). The nurseries were closed and temporary ones established on

the obstetric floor, all contacts were discharged as quickly as possible and followed at home by their respective physicians, and the infants with the disease were removed to the pediatric ward of the hospital. None of the infants in the pediatric unit, who ranged in ages from 1 to 18 months, developed diarrhea although they were confined in the same general unit with the affected newborn infants. Shortly after the nurseries, which had been thoroughly cleaned after the discharge of all of the exposed infants, were reopened, single mild cases of diarrhea developed at intervals of several days. These infants were isolated promptly even though they did not appear ill; they responded satisfactorily to a modification of the feeding formula and their courses were uneventful. However, these infants undoubtedly had mild epidemic diarrhea of the newborn and transmitted the causative agent to other infants. Complete control of the epidemic was not obtained until the entire department was closed to admissions and was thoroughly cleaned and repainted before it was reopened.

During the relatively long period of time under observation there was a total of 346 infants in the nurseries, of whom 63 developed diarrhea of varying intensity. The morbidity rate was 18.2 per cent. The incidence of the disease, however, was higher among the premature infants than among the full-term ones; six of nine infants in the premature nursery and five of twenty-one infants, ranging in weight from 5 pounds to 5 pounds, 8 ounces, in the other nurseries developed the disease. The average case fatality rate was 23.8 per cent, but it, too, was higher among the premature infants than among those of full-term gestation; 83 per cent (five of six) of the small premature infants, 20 per cent (one of five) of the larger premature ones, and 17.3 per cent (nine of fifty-two) of the full-term infants died from the disease. Only 8.7 per cent of the exposed infants weighed less than 5 pounds, 8 ounces, but 36.6 per cent of them developed the disease and in this group of infants 40 per cent of the deaths occurred (Table I).

TABLE I. SUMMARY OF INFANTS AFFECTED WITH EPIDEMIC DIARRHEA OF THE NEWBORN

	TOTAL	FULL-TERM INFANTS	PREMATURE INFANTS		
			UNDER 5 POUNDS	OVER 5 POUNDS	TOTAL
Contacts	346	316	9	21	30
Disease	63	52	6	5	11
Deaths	15	9	5	1	6
Nonfatal cases					
Severe	17	13	1	3	4
Moderate	6	5	0	1	1
Mild	25	25	0	0	0
Morbidity (per cent)	18.2	16.5	66.0	23.8	36.6
Case fatality	23.8	17.3	83.0	20.0	54.5

The ages of the infants at the onset of the disease ranged from three to twenty-two days for the full-term and from five to seventeen days for the premature infants. Since there were multiple contacts for these infants, it is impossible to estimate the incubation period, but its maximum could not exceed the age of the patient at the time of the onset of symptoms. In fifty-one instances the disease was manifest while the infant was still in the nursery while twelve

of them were readmitted to the hospital after developing the disease at home. Three of these, however, had unexplained weight loss in the hospital before discharge, which might have been interpreted as an early symptom of epidemic diarrhea of the newborn. Five of the infants who were readmitted and ten (including five premature infants) remaining in the hospital died.

The only symptom which most of the infants with the mild disease had was loose stools, and the duration of the diarrhea ranged from one to five days; none of these infants had a carbon dioxide combining power lower than 35 volumes per cent, and only four of them lost more than 10 per cent of their birth weight during the hospital course. Among the others the symptoms were more severe; many of them had vomiting and precipitous loss of weight in addition to the diarrheal stools, the duration of which was longer than in the mild cases and ranged from two to seventeen days. All of this latter group had acidosis, which was demonstrated by the determination of a low carbon dioxide combining power. The lowest carbon dioxide determination was 6 volumes per cent, and the greatest weight loss was 31 per cent of birth weight. Eight of the infants had thrush and six, impetigo neonatorum before the onset of the diarrhea or during its course. Two of the infants had both thrush and impetigo. One infant developed osteomyelitis of the femur, another had thrombophlebitis of the saphenous vein, and a third suffered from a terminal sclerema. It was suspected that one of the infants had a congenital heart lesion, which may have contributed to his death. One infant who had septicemia and bowel obstruction with peritonitis developed melena before death.

Cultures were obtained from the stools of the patients, from the nasopharynx of the patients and of attending physicians, nurses, and maids, from the formulas and their ingredients in the formula kitchen, and from blood agar plates exposed to the air for thirty-minute periods in the nurseries, private rooms, wards, formula kitchen, delivery room, labor room, corridors, and nurses' stations. Eighty-six stool cultures were obtained from twenty-nine different patients, eleven nasopharyngeal cultures from patients, and thirty-seven nasopharyngeal cultures from members of the staff. One hundred and eight agar plates were exposed during this period in the places specified. None of these showed growth of a recognizable pathogenic bacterium. Among sixteen blood cultures, coliform bacilli were recovered in four instances in each of which there was also the clinical picture of septicemia. Unfortunately it was not possible to perform virologic studies. There were no herpetic lesions noted in the mouths of any of the infants affected with diarrhea.²

Autopsy examinations of ten of the infants did not demonstrate any lesions sufficiently characteristic to differentiate them from those of other forms of enterocolitis. Acute passive congestion of the viscera and terminal pneumonia were found in many of them.

CLINICAL COURSE

Fifty-two patients had a fairly characteristic clinical course, the severity of which ranged from mild diarrhea with no other symptoms to severe diarrhea with marked acidosis, dehydration, prostration, and death in seven instances.

Of eleven patients who had recurrent periods of diarrhea, nine suddenly developed a state of collapse and eight died within a few hours. Six of the infants with this type of clinical course weighed less than 5 pounds, 8 ounces at birth. We have chosen to designate this type of clinical course in epidemic diarrhea of the newborn as "biphasic."

The first phase of this course consisted in the development of diarrhea with moderately severe associated symptoms of dehydration, acidosis, and prostration. After three to five days the character of the stools tended to improve but they did not become entirely normal. However, there were better feeding habits, absence of acidosis, gain of weight, and a better general appearance.

This improvement lasted only a few days and was supplanted by a recurrence in which the acidosis tended to be more severe, the diarrhea more frequent and severe, and the infant obviously more critically ill. In spite of a good oral intake augmented with large amounts of parenteral fluids, the infant would continue to lose weight. After a few days the character of the stools tended to improve and some of them appeared normal. There was sometimes gain of weight, but the general appearance of the infant was not encouraging. After twenty to forty-eight hours of this "pseudo-improvement," the infant suddenly, sometimes within fifteen minutes, went into a state of profound collapse characterized by periods of apnea, weak respirations, evidence of cardiac dilatation, collapse of the peripheral vascular bed, abdominal distention, cyanosis, and death within a few hours. Stimulants and fluids, including adrenal cortical extract and plasma, were ineffective when this state of collapse was reached, except in two instances in each of which improvement occurred when a large quantity of plasma was given rapidly as an intramedullary infusion. The first infant recovered after the injection of almost 300 c.c. of plasma and the second after 200 c.c., only to die in a similar episode one week later.

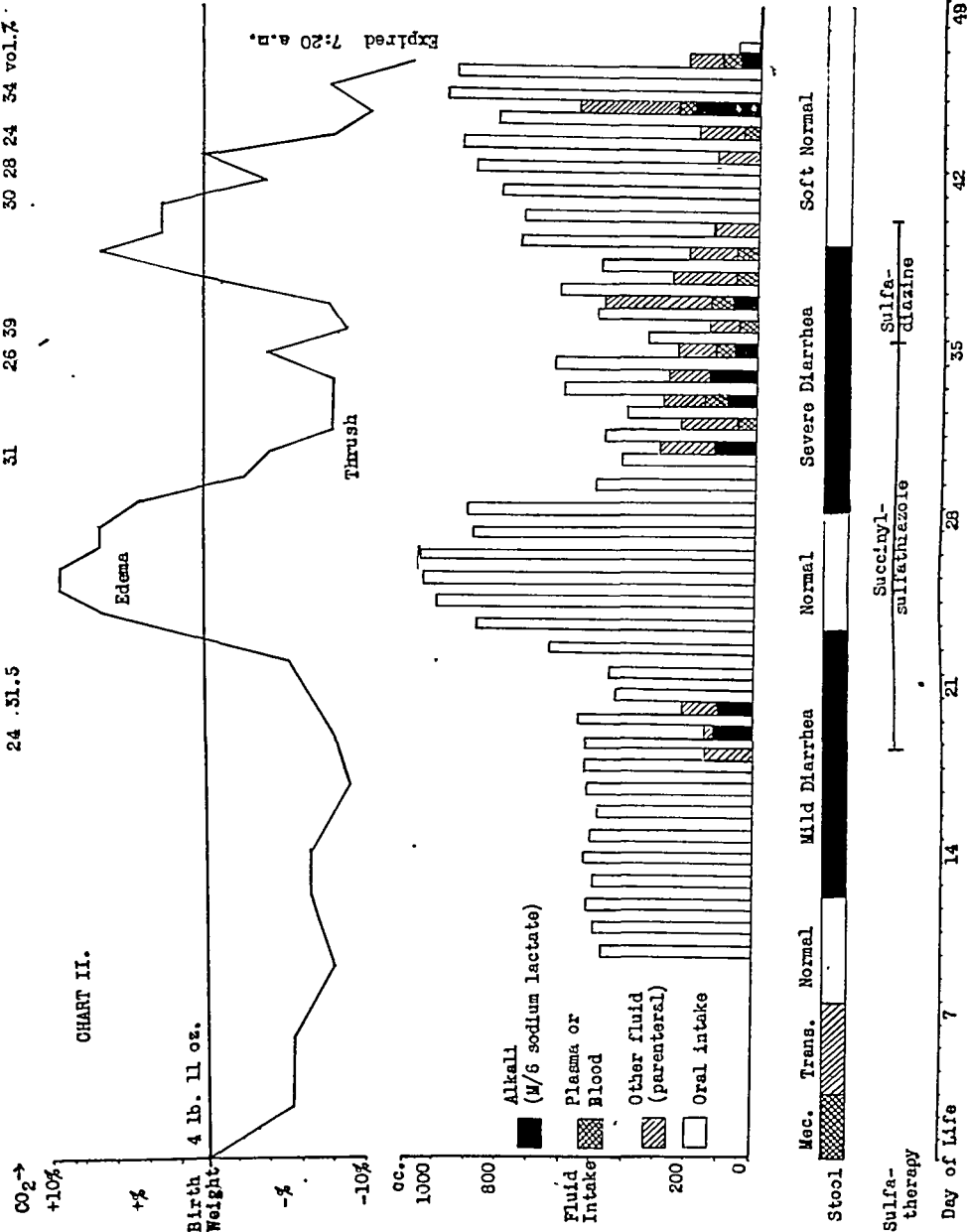
The following case report is illustrative of this type of clinical course:

CASE REPORT

Baby S., a Negro female, weighed 4 pounds 11 ounces at birth; she appeared to be a vigorous premature infant. Her course was uneventful until the twelfth day of life when she occasionally had a loose stool, but never more than one during a twenty-four-hour period. She did not appear ill, and modification of her feeding seemed to control this diarrheal disturbance. To counteract a failure to gain weight satisfactorily she was given a hypodermoclysis of lactate-Ringer's solution.

The first phase of her clinical course of diarrhea began on the nineteenth day of life when she passed another loose stool and had an acidosis (carbon dioxide combining power of 24 volumes per cent) without clinical symptoms, which was corrected by the subcutaneous administration of a calculated amount of one-sixth molar sodium lactate. Later that day her stools became green and liquid; some of them were expelled explosively. She was removed to the Isolation Nursery, but the following day her stools improved in character and became normal during the next few days. Succinylsulfathiazole (0.25 Gm. daily) was administered orally, and fluid was given parenterally on two occasions. Her general course was uneventful until the twenty-sixth day of life when she began slowly to lose weight from a maximum of 5 pounds. She had had a slight degree of edema, and it was thought that the weight loss might have been accounted for by the disappearance of the edema. Oral moniliasis developed on the twenty-ninth day of life.

The second phase of disease began on the twenty-ninth day of life when she passed a few diarrheal stools. Marked dehydration and acidosis developed rapidly and parenteral fluids, including alkalis, crystalloid solutions, and plasma, were given immediately. There was peripheral vascular collapse, the respirations were rapid and shallow, dehydration was severe, the diarrheal stools were expelled explosively, the abdomen was markedly distended, and there was a moderate degree of cyanosis. After three days the character of the stools was considerably improved, being loose at one time and normal at another. Fluids were administered parenterally, and on the thirty-sixth day of life sulfadiazine was substituted



for succinylsulfathiazole. By the thirty-ninth day of life the stools were normal, the weight had again reached almost 5 pounds, and she entered the period of "pseudo-improvement." Although she took as much as 900 c.c. of formula daily, her general appearance and activity were not encouraging. She began to lose weight in spite of normal stools and of apparently adequate fluid intake. Abdominal distention was severe, and it did not respond to the usual therapeutic measures. On the forty-eighth day of life she suddenly went into a state of shock. Her respirations became short and shallow with occasional long periods of apnea. A loud systolic apical murmur, which had not been heard previously, was audible now. There were peripheral vascular collapse, cyanosis, and listlessness. She did not respond to oxygen, plasma, other fluids, adrenal cortical extract, or stimulants and died from respiratory failure within four hours of the onset of these symptoms (Chart II).

The autopsy revealed an emaciated and dehydrated Negro female infant with a moderately distended but not tense abdomen. The small and large bowels were distended with gas and with liquid fecal matter. Histologically, there was a mild acute enterocolitis, for which there was little gross evidence except for several small indefinite areas of mucosal and serosal hyperemia interspersed between areas of healthy bowel. Other significant findings included subepicardial petechiae and toxic myocardiosis; pulmonary atelectasis, interstitial pneumonitis, and early bronchopneumonia; congestion of the liver with mild fatty metamorphosis; congestion of the spleen; toxic nephrosis; inflammatory hyperplasia of the lymph nodes; and interstitial edema of the pancreas and of the thymus.

THERAPY

Epidemic diarrhea of the newborn requires prompt administrative and medical attention for its control. A careful survey should be instituted to seek the cause of the outbreak, and a regimen of treatment outlined for the care of the patients. Affected infants must be isolated, exposed ones segregated, and a new unit, removed from the contaminated obstetric floor, provided for the newborn infants; each group must have a separate nursing staff. Medical supervision and laboratory facilities must be available throughout the day and the night. The treatment of ill infants should include modification of the oral feeding, maintenance of fluid balance, prompt correction of states of acidosis, oral administration of synthetic ascorbic acid and thiamine chloride, and intravenous injections of plasma or of whole blood when indicated.

Attention has already been directed to the significance of weight loss as a symptom which may precede the onset of diarrhea. During this epidemic the practice of weighing the infants in the morning and again in the evening permitted an early recognition of weight loss and prompt administration of parenteral fluid to combat it. Even the infants who take large quantities of fluid orally may need almost equally large amounts of fluid parenterally. On the other hand, marked gain in weight may precede the appearance of demonstrable edema, and its detection warn of the need for plasma or whole blood to prevent fluid retention. The determination of the hemoglobin for detection of hemoconcentration or hemodilution should be employed, since reliance upon the clinical impression alone is frequently not sufficient for an adequate appraisal of the patient's state of hydration.

A large number of the infants received succinylsulfathiazole (0.13 Gm. per pound of body weight per day) either as a prophylactic or a therapeutic measure, but it did not appear to prevent the development or to alter the course of the disease. Many of the infants refused or regurgitated the fluid with which

the drug was mixed, and the stools of the noninfected infants became more mucoid than normal. An absorbable sulfonamide, sulfathiazole or more frequently sulfadiazine, was given to eleven patients, of whom three had a complicating infection for which it was indicated. Its administration, however, did not seem to alter the course of the diarrheal disturbance. Adequate fluid intake and output and alkalinity of the urine must be maintained while sulfonamides are used.

Penicillin was given intramuscularly to six infants in dosages of 50,000 to 100,000 Oxford units daily. In none was the diarrheal disease altered, but the treatment was of value for other coexisting infection. In instances in which septicemia is suspected, it is advisable to use both an absorbable sulfonamide and penicillin since *Escherichia coli*, a penicillin-resistant organism, frequently invades the blood stream.

Perhaps vitamin K should be administered to these patients empirically, in order to prevent any bleeding tendency due to hypoprothrombinemia. It is possible that during the diarrheal disturbance there is an interference with the synthesis of the vitamin by the normal intestinal flora. Vitamin K has been advised as an adjunct to succinylsulfathiazole therapy.³ Although adrenal cortical extract has been recommended for the treatment of shock, our clinical experience is in accord with that of others who have previously reported the lack of a favorable effect.

USE OF GAMMA GLOBULIN

Gamma globulin* was given to twenty-eight patients. An intramuscular injection of 5 c.c. of gamma globulin was given to each of fourteen infants who had epidemic diarrhea of the newborn or who were suspected of having the disease at that time. An injection of 5 c.c. of gamma globulin was given to fourteen infants who had been exposed to the disease while there were twenty-seven other infants in the nursery who did not receive the injection (Table II).

TABLE II. ADMINISTRATION OF GAMMA GLOBULIN TO INFANTS WITH EPIDEMIC DIARRHEA OF THE NEWBORN

	CONDITION OF THE INFANT AT THE TIME OF THE ADMINISTRATION OF GAMMA GLOBULIN*				CONTROL GROUP†
	NO EVIDENCE OF DIARRHEA	SUSPICIOUS OF DIARRHEA	EPIDEMIC DIARRHEA	TOTAL	
Total No.	14	5	9	28	27
Results:					
No diarrhea at any time	9	0	0	9	22
Suspicious of diarrhea	3	1	0	4	4
Epidemic diarrhea of the newborn	2	4	9	15	1
Died	1	1	0	2	0

*Each infant received 5 c.c. of gamma globulin intramuscularly, except one of those who had the disease, who received 10 c.c.

†Infants exposed to epidemic diarrhea of the newborn who did not receive gamma globulin.

*The products of plasma fractionation employed in this work were prepared by the Department of Physical Chemistry, Harvard Medical School, Boston, Mass., from blood collected by the American Red Cross, under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Harvard University.

In this small group none of the infants to whom the product was given as a therapeutic agent improved within a short time after its administration, and more cases of diarrhea developed in the group who received it as a prophylactic agent than in the control group. None of the infants who received gamma globulin developed any local or general reaction following its administration intramuscularly.

DISCUSSION

In this outbreak of epidemic diarrhea of the newborn a number of problems were encountered. Of great importance among these were the ones relating to the detection of the disease and its cause. The mild cases of diarrheal disturbance which developed as the earliest instances in the outbreak were not recognized as epidemic diarrhea of the newborn. Only when more infants were affected, and among them infants with more serious disease, was the insidious onset of the outbreak determined in retrospect. This problem of early diagnosis, could it be solved, would certainly diminish the number of infants inadvertently exposed to the infection and consequently the magnitude of an outbreak. As has been stated previously, whenever the development of diarrheal stools cannot be easily explained on some other noninfectious basis, it would seem advisable to isolate the newborn infant and to consider as a provisional diagnosis epidemic diarrhea of the newborn whenever two or more infants are similarly affected. Such a plan of procedure may abort an impending outbreak of the disease.

To prevent an outbreak of epidemic diarrhea of the newborn is admittedly more important than to detect it. The cause of this outbreak could not be determined from the investigative procedures which were employed. It may be significant that at approximately the same time there was an outbreak of epidemic diarrhea, nausea, and vomiting of unknown cause⁴ in Philadelphia among adults. Lyon and Folsom⁵ have reported an epidemic of diarrhea of the newborn in a community where influenza was concurrently epidemic. In their series, benefit was obtained from the administration to the infants of blood serum from patients convalescing from the influenzal infection, but no beneficial effect was noted when blood from normal adults was injected. Whether any etiologic relationship among these conditions exists is not known. The best supported evidence up to the present time for an etiologic agent for epidemic diarrhea of the newborn is that submitted by Light and Hodes⁶ in favor of a virus. Unfortunately, we were not equipped to pursue virologic studies during this outbreak. None of the studies which were performed bacteriologically revealed a causative agent. Furthermore, there were no characteristic lesions identified in the pathologic specimens from those infants who were examined postmortem.

Complete control of the outbreak was not obtained until the entire obstetric floor was closed to admissions, thoroughly cleaned, and repainted before it was reopened. Initially the nurseries were closed and temporary ones established elsewhere on the same floor. Other portions of the hospital were already overcrowded with medical and surgical patients, and it was not desired to admit

obstetric patients to those divisions. When a second wave of the disease developed, however, the entire floor was closed to admissions and temporary quarters for the obstetric department established elsewhere in the hospital and staffed by a nursing personnel which was absolutely separate from that charged with the care of the affected and the exposed infants. Since the reopening of the cleaned and repainted department, there have been no instances of this disease among the infants in the nursery.

Epidemic diarrhea of the newborn must always be regarded as a serious disease. Among twenty-eight infants treated for this disease in 1943, there was one death, that of a premature infant. Among sixty-three affected infants in 1944 there were fifteen deaths, of which six were premature infants. In our experience during this more recent outbreak we found that the outcome was less favorable among the small and the premature infants affected with the disease and among the infants who showed a "biphasic" course. It could not be ascertained whether these were instances of relapse or of infection with another microorganism, but the former seems more likely. Significant of poor prognosis are such findings as poor general appearance, persistent diarrhea even if mild, persistent weight loss in spite of a tremendous fluid intake (orally and parenterally), intractable abdominal distention, bleeding tendencies, precipitous weight loss, the appearance of the "biphasic" course, prematurity, complications, and collapse.

In the treatment of this disease the importance of maintenance of hydration and of acid base balance is emphasized again. As previously recommended, chemical evidence regarding acidosis should be sought in all instances in which the infant shows any deviation from the normal pattern since a severe degree of acidosis may be present in the absence of significant clinical signs, which would otherwise not be detected nor treated adequately. The sulfonamides and penicillin did not appear to be effective in the treatment of epidemic diarrhea of the newborn; this is understandable if the etiologic agent is proved to be a virus. Our experience with gamma globulin is limited, and the number of patients treated in this manner is too small to warrant any definite conclusions regarding its value. In the dosage used (5 c.c.) gamma globulin did not retard the development of the disease among infants already exposed to it or alter detectably its clinical course. The role of gamma globulin as an adjunct to the therapy of epidemic diarrhea of the newborn should be investigated further, possibly with larger doses of the product than have been used.

SUMMARY

In an outbreak of epidemic diarrhea of the newborn involving sixty-three infants, there were fifteen deaths. The incidence of the disease and the death rate were higher among the premature infants.

In eleven instances a biphasic clinical course was encountered, in which after clinical and biochemical improvement there suddenly developed ominous symptoms with a state of collapse and death for eight of the infants.

Control of the outbreak was not obtained until the entire department was closed to admissions and thoroughly cleaned before it was reoccupied. An etiologic bacterial agent was not discovered, and virologic studies could not be performed.

Therapeutic measures included maintenance of hydration, correction of acidosis, modification of feeding, and administration of amino acid solution, plasma, and whole blood. Neither sulfonamide nor penicillin therapy seemed to influence the clinical course of epidemic diarrhea of the newborn, and in a limited series the intramuscular administration of gamma globulin had no apparent prophylactic or therapeutic effect.

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A STUDY OF PREMATURE INFANTS OBSERVED IN A PRIVATE HOSPITAL BEFORE AND AFTER THE ESTABLISHMENT OF A PREMATURE NURSERY

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PREMATURE births accounted for 46 per cent of neonatal deaths in the United States in 1941.¹ When the premature neonatal deaths are drastically reduced in a large private maternity hospital through the establishment of a premature nursery, it is interesting to examine the records of those premature infants and to point out the factors that have produced this reduction.

This study was made on a consecutive series of 319 premature infants delivered in the St. Joseph's Maternity Hospital in Houston, Texas, during the period of December, 1942, to December, 1944. On Dec. 1, 1943, a premature nursery was opened in one wing on the top floor of the hospital. The nursery was well isolated from the maternity section and the pediatric department which were located in the same building. The nursery was equipped with ultra-violet lights for protection from air-borne infections. No one with the exception of the nursing personnel was allowed in the main nursery. All examinations by physicians were made in a separate examining room equipped for that purpose. Special nurses trained in the handling of premature infants were employed to care for the infants. At times student nurses have assisted in the care. Warm incubators were kept in the delivery rooms, ready for each premature infant. Oxygen was ordered given routinely until discontinued by the physician or pediatrician in charge.

In the year's period before the opening of the premature nursery there were 160 premature infants delivered, weighing 5 pounds or less. Of this number there were 87 male infants and 73 female infants representing a sex ratio of 120, whereas 106 is the usually quoted term sex ratio. Forty male infants and 48 female infants lived, giving a survival rate of 46 per cent and 66 per cent respectively. As shown in Table I, 54 per cent of the male infants and 34 per cent of the female infants died.

In the year's period after the opening of the premature nursery there were 159 premature infants delivered. Of this number there were 80 male infants and 79 female infants, a sex ratio of 101. Sixty-one male infants and 63 female infants lived, giving a survival rate of 76.2 per cent and 79.7 per cent, respectively. It will be seen in Table II that 23.8 per cent of the male infants and 20.3 per cent of the female infants died.

Since the opening of the nursery there has been a decrease in total premature mortality from 45 per cent to 22 per cent. This represents an annual saving to the community of 36 infants, and inasmuch as each infant is said to be of \$9,000 value² to the community, this represents a yearly salvage of \$324,000.

TABLE I. PREMATURE INFANTS DELIVERED FROM DECEMBER, 1942, TO DECEMBER, 1943

	TOTAL	MALE	FEMALE
Number	160 (100%)	87 (54%)	73 (46%)
Number living	88 (55%)	40 (46%)	48 (66%)
Number dead	72 (45%)	47 (54%)	25 (34%)

TABLE II. PREMATURE INFANTS DELIVERED DECEMBER, 1943, TO DECEMBER, 1944

	TOTAL	MALE	FEMALE
Number	159 (100%)	80 (50.3%)	79 (49.8%)
Number living	124 (78%)	61 (76.2%)	63 (79.7%)
Number dead	35 (22%)	19 (23.8%)	16 (20.3%)

TABLE III. SUMMARY OF DEATHS

YEAR	DELIVERIES	INFANT DEATHS	FULL-TERM DEATHS	PREMATURE	NONVIABLE
1943	5,100	105 (2.6%)	23 (22%)	61 (58%)	21 (20%)
1944	5,036	64 (1.2%)	18 (28%)	38 (59%)	8 (13%)

Table III shows the effect of the decrease in premature deaths on the percentage of total infant deaths in the hospital after the establishment of the nursery.

The percentage of total deaths has dropped from 2.6 per cent in 1943 to 1.2 per cent in 1944. These percentages include all births, viable and nonviable. In this period there was no decrease in the percentage of deaths in term infants, actually a small increase, so that the decrease in total infant deaths was directly due to the salvage of prematurely born infants. There was a significant decrease in the number of nonviable infants born. The number of premature infant deaths was reduced by 36, although the percentage of premature deaths to the total infant death rate remained approximately the same.

Table IV shows the weights at birth in the two-year period 1942 to 1944. It includes the outcome to the infants in each weight group.

TABLE IV. WEIGHTS AT BIRTH

YEAR	1 TO 2 POUNDS		2 TO 3 POUNDS		3 TO 4 POUNDS		4 TO 5 POUNDS	
1943	Total 20		14		36		85	
	Living 0	Dead 20	Living 2	Dead 12	Living 16	Dead 20	Living 70	Dead 15
1944	Total 5		19		40		95	
	Living 0	Dead 5	Living 5	Dead 14	Living 29	Dead 11	Living 90	Dead 5

There has been a significant decrease in the number of infants delivered weighing less than 2 pounds. It has been claimed that the war had some bearing on the large number of very small infants and abortions. On the other hand, with the establishment of the premature nursery, and with obstetricians being particularly interested in obtaining larger infants, the decrease in the number of very small infants is in great measure due to their efforts. They have accomplished this by postponing induction of labor in toxemic patients, and those with placenta previa until the fetus is more certainly viable.

There has been a decrease in the deaths of infants in the 3- to 5-pound group. Great credit for this decrease is due, of course, to the nursing personnel. Also the use of sulfonamides and penicillin, and the introduction of the routine use of oxygen, as later shown, are believed to have had their effect on this reduction.

Table V shows the time of deaths of the premature infants in this series.

TABLE V. TIME OF DEATHS OF PREMATURE INFANTS

YEAR	UNDER 24 HOURS	UNDER 48 HOURS	UNDER 96 HOURS	OVER 96 HOURS
1943	38 (53%)	4 (6%)	5 (7%)	25 (34%)
1944	20 (58%)	5 (14%)	5 (14%)	5 (14%)

The increased use of penicillin and of sulfadiazine had some beneficial influence on the mortality rate in 1944. In 1943 seven infants had sulfadiazine or penicillin and 62 deaths occurred. Only two of the infants who died had had a sulfonamide. In 1944, 31 infants had a sulfonamide derivative or penicillin and only 35 deaths occurred; of the 35 deaths only 5 occurred after 96 hours of life. Approximately four times the number of infants had penicillin or a sulfonamide in 1944 as in 1943, and the incidence of mortality has been cut more than 50 per cent.

Table VI shows the type of feedings and mortality.

TABLE VI. TYPES OF FEEDINGS

YEAR	BREAST MILK		COW'S MILK FORMULA	
	LIVING	DEAD	LIVING	DEAD
1943	51 (91%)	5 (9%)	33 (60%)	23 (40%)
1944	69 (91%)	7 (9%)	47 (87%)	7 (13%)

In both years the premature infants given breast milk showed a consistently higher rate of survival as compared with those given a cow's milk formula. Breast milk was particularly effective as compared with cow's milk formula before the premature nursery was opened. The establishment of a breast milk bank in this hospital, so that breast milk was available at all times for premature infants, has been of considerable value.

TABLE VII. INFANTS RECEIVING OXYGEN

YEAR	NUMBER RECEIVING OXYGEN	DEATHS
1943	113 (71%)	72 (45%)
1944	156 (98%)	35 (22%)

The routine use of oxygen, or an oxygen and helium mixture, until discontinued by a physician, was employed in the year, 1944, in which there was a sharp reduction in deaths of premature infants. The start of oxygen therapy was not waited until the infant developed cyanosis.

COMMENT

Rascoff³ reported that with the establishment of a premature nursery in an obstetrical hospital the premature infant mortality rate was reduced 55

per cent. The establishment of a premature nursery in a large maternity hospital in Houston, Texas, resulted in a decrease of 51 per cent in the premature infant mortality rate. The training and interest of the nursing personnel have been great factors in this reduction. This has been well recognized in the past. Certain other factors can be of value in the reduction of the mortality in this type of infant. The interest of the obstetrician in obtaining a larger and more certainly viable infant is of great importance. Premature infants given breast milk, both before and after the start of the nursery, in this series showed the greater chance of survival. The group of infants receiving treatment with one of the sulfonamides or penicillin had the lower mortality. The year the premature infants received oxygen routinely from birth until discontinued by physician showed the lower mortality rate.

SUMMARY

The premature infant mortality rate was reduced 51 per cent in a large maternity hospital through the establishment of a premature nursery.

The factors operable in this reduction have been indicated to be:

- A. The training and interest of the nursing personnel
- B. The interest of obstetricians in obtaining larger and more certainly viable infants
- C. The use of breast milk as the initial feedings for the premature infants
- D. The routine use of oxygen immediately after delivery without waiting for the development of cyanosis
- E. The use of a sulfonamide or preferably penicillin routinely in all instances of atelectasis or in infants of mothers having immediate prenatal infections
- F. The institution of aseptic nursery technique together with ultraviolet irradiation to prevent air-borne infections.

The economic value of a premature nursery to a hospital and community, to mention nothing of the saving of mental anguish to numbers of individuals, is in direct proportion to the number of premature infants delivered in that institution.

I wish to thank Dr. A. L. Dippel for his many valuable suggestions in the preparation of this report.

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SALMONELLA CHOLERAESUIS (VARIETY KUNZENDORF) BACTERIEMIA COMPLICATING STREPTOCOCCAL SORE THROAT

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THE investigations into the antigenic structure of the paratyphoid bacilli have greatly stimulated clinical interest in human salmonellosis. It is now firmly established that *Salmonella* infections in man are much more common than it was believed even a decade ago, that many of the more than 100 different species belonging to the genus may cause disease, and that various species are responsible for any of the three clinical syndromes, namely, (1) *Salmonella* fever, (2) *Salmonella* septicemia or bacteriemia and (3) *Salmonella* gastroenteritis or enterocolitis.

Attention has been called in the past to the fact that *Salmonella* bacteriemia may develop following other maladies. It is likely that in some instances the two diseases were independent of each other. In other cases, however, a pathological process or operative procedure may have caused a decrease in the resistance of the individual to the *Salmonella* organism and thus contributed to its invasion of tissues and blood. Moreover, the changes brought about by the paratyphoid bacillus may be masked by the other infectious process and thus escape proper recognition. The relationship between salmonellosis and preceding or concomitant diseases is worthy of further study. For this reason, a case of *Salmonella choleraesuis* (variety Kunzendorf) bacteriemia complicating or concurrent with streptococcal sore throat is presented here.

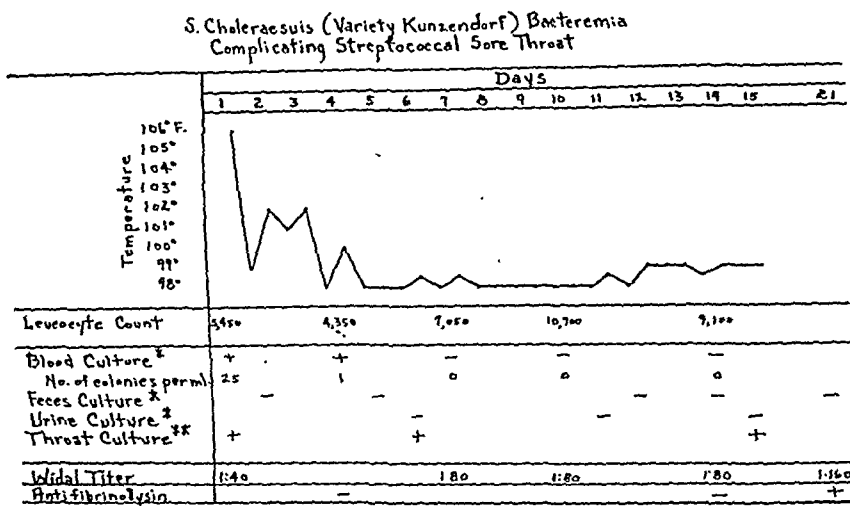
REPORT OF A CASE

R. S., a 10-year-old white male, was admitted on June 30, 1945, to the Pediatric Service of Drs. Marvin Israel and Norman C. Bender of the Children's Hospital. The past history revealed that the patient had had measles and frequent attacks of tonsillitis. Two days prior to admission the patient complained of headache and malaise. He had fever and also emesis on one occasion. On admission the temperature was 105.6° F., the pulse rate, 110 per minute, and the respiratory rate 40 per minute. The pertinent findings on physical examination were as follows: The tonsils showed numerous ulcerative lesions and were covered with purulent exudate. The anterior cervical lymph nodes were enlarged. No further abnormalities were noted. The urine was normal. Kahn, tuberculin, and Schick tests were negative. The spinal fluid, obtained on the second hospital day, was found to be normal. On the basis of these findings the patient was treated for acute sore throat. Sulfadiazine (1 grain per pound of body weight per twenty-four hours) was given by mouth. The throat was irrigated with warm saline solution. On the second hospital day the temperature of the patient was 102° F.; the patient became comatous and, for several hours, presented a shocklike picture. For that reason, glucose (5 per cent) in physiologic saline solution was given intravenously and sodium sulfadiazine (1 grain per pound of body weight per twenty-four hours) was administered subcutaneously. His condition improved. Sulfadiazine therapy by mouth was resumed on the third day and continued until the eleventh hospital day. The patient made a complete recovery.

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The throat culture on admission revealed the presence of numerous hemolytic streptococci. A blood culture taken at that time proved to be positive for *S. choleraesuis* (variety Kunzendorf); there were 25 colonies per cubic centimeter of blood. On the basis of these laboratory findings, a diagnosis of streptococcal sore throat concomitant with or complicated by *S. choleraesuis* bacteremia was made.

The accompanying chart (Fig. 1) presents the pertinent findings throughout the course of the illness.



+ = for *S. choleraesuis*
++ = for hemolytic streptococci

Fig. 1.

One week after discharge from the hospital the patient was seen at the Out-Patient Department. The patient complained of sore throat. The throat was injected. No other pathologic findings were obtained on physical examination. The throat culture revealed the presence of scattered hemolytic streptococci. Antifibrinolysin was present in the blood. The patient's serum agglutinated *S. choleraesuis* (variety Kunzendorf) in a dilution of 1:160. Culture of the feces was negative for *Salmonella*.

Two weeks later, Aug. 5, 1945, the patient developed diarrhea which lasted for one day. It is said that blood and mucus were not present in the feces. He was seen on the following day. At that time the throat was still injected; no other abnormalities were noted on physical examination. The throat culture showed scattered hemolytic streptococci. Antifibrinolysin was still present in the patient's serum. A culture of the feces was negative for *Salmonella*. The titer of agglutinins for the homologous microorganism was 1:160.

DISCUSSION

Recent reports in the literature indicate that *Salmonella* bacteremia or septicemia may develop as a complication of other maladies. In 1937, in a review of the literature and his own observations on *Salmonella suispestifer* infection of man, Harvey¹ pointed out that this disease may be associated with other illnesses such as tuberculosis, pharyngitis, cystitis, rheumatic heart disease, myomas of the uterus, hypernephroma, rickets, and congenital heart disease. Since then, several reports have been published indicating that certain pathologic processes may favor the invasion of the blood by *Salmonella*

organisms. Four patients observed by Jager and Lamb² were debilitated prior to the onset of the *Salmonella* infection, either by previous illness or chronic alcoholism. An excellent illustration for this mode of pathogenesis of *Salmonella* infection is the case observed by Ravitch and Washington.³ This patient developed *Salmonella* bacteriemia and meningitis secondary to meningococcal meningitis. In 1942, Neter reported a case of *S. choleraesuis* bacteriemia complicating scarlet fever. It was assumed that the hemolytic streptococcal infection predisposed to the secondary infection by a strain of *S. choleraesuis* of low virulence, but empowered with invasiveness. Analogous conditions probably existed in the case presented in this communication. The diagnosis of streptococcal sore throat in the present case is based on the clinical findings, the presence of numerous hemolytic streptococci in the throat, and the development of antifibrinolysin during the course of the illness. The diagnosis of *Salmonella* bacteriemia was made solely on the basis of routine blood culture examinations. This organism, which was identified by Dr. Erich Seligmann of the New York Salmonella Center, was recovered on two occasions. On the day of admission, 25 organisms per cubic centimeter were present in the blood. Three days later the number of bacteria had decreased to one per cubic centimeter of blood. Compatible with the diagnosis of *Salmonella* bacteriemia is the observation that leucopenia persisted in spite of the concurrent streptococcal infection. It is interesting to note in this connection that, according to Harvey,¹ in adults who suffered from *Salmonella* infection and an associated disease the white cell count varied according to the nature of the accompanying illness. Leucocytosis existed in the two patients suffering from *Salmonella* bacteriemia concurrent with scarlet fever and meningococcal meningitis, respectively (Neter^{4, 5}).

It is the experience of all observers that the primary focus of infection in sporadic cases of *Salmonella* bacteriemia usually cannot be discovered. Throat, feces, and urine cultures on the patient reported herein failed to reveal the presence of *Salmonella* organisms. No evidence was obtained that diarrheal disease existed among the relatives or possible contacts prior to the illness of this patient.

The question arises as to whether or not the invasion of the blood stream by *S. choleraesuis* took place from the throat which was infected by hemolytic streptococcus. As mentioned before, a search for paratyphoid bacilli in the material obtained from the infected tonsils failed entirely. Recent investigations by Varela and Olarte⁶ as well as Hormaechea and Peluffo⁷ prove beyond doubt that *Salmonella* organisms may be present in the oral cavity, in carriers and patients with *Salmonella* infection. In the latter instance, the oral cavity may be the primary focus of infection or the organ of elimination of the microorganism.

A study of the antibody response of the present case revealed the development of agglutinins in only moderately high titer. The serum of the patient obtained on the day of admission to the hospital caused agglutination of the homologous organism in a dilution of 1:40. At that time *S. choleraesuis* was present in the circulating blood. Three weeks later the titer was 1:160.

This titer may be considered significant, particularly in view of the observations of Gouldner, Kingsland, and Janeway⁸ to the effect that the sera of thirty-four normal subjects failed to agglutinate *S. choleraesuis*. Rubenstein, Feemster, and Smith⁹ found an increase in titer of agglutinins in 42 per cent of fifty patients suffering from group C *Salmonella* infections. That agglutinins in high titer may develop in some patients with *Salmonella* infections is evidenced by the observations of Seligmann, Saphra, and Wassermann,¹⁰ who encountered titers up to 1:6,400. However, not all patients with *Salmonella* infections, or even *Salmonella* bacteriemia, develop demonstrable antibodies against the homologous microorganism (Jager and Lamb,² and others).

SUMMARY

A case of *S. choleraesuis* (variety Kunzendorf) bacteriemia complicating or concomitant with streptococcal sore throat is described. The relationship of the two diseases is discussed.

The authors wish to express their appreciation to Dr. Erich Seligmann, New York Salmonella Center, for identification of the *Salmonella* organism.

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PRELIMINARY OBSERVATIONS ON SOME CHILDREN WITH RHEUMATIC HEART DISEASE TRANSPORTED TO A SUBTROPICAL CLIMATE

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COBURN¹ very effectively called attention to the helpful climatic effects in children with recurrent rheumatic fever; this was soon followed by Roche and Jones² bringing some half dozen rheumatic cardiac children from Boston to Miami Beach during the winter months for three years. The problem of the transportation of rheumatic fever patients to a subtropical climate³ is not a simple nor sure one. Nichol⁴ has shown in a study of the geographic distribution of rheumatic fever in the United States that the rate in southern Florida is about one-tenth that of the average northern rate. On the other hand, rheumatic recurrences do occur in an ideal tropical climate⁵ and rheumatic heart disease exists among native Miami children.

This preliminary report is based on eighty-eight children, from 6 to 16 years old, who were brought to Miami from 1938 to 1945 and spent a total of 114 patient-years in the National Children's Cardiac Home amid sanitarium surroundings. Very likely, at least 1,000 patient-years will be necessary to form statistical conclusions within a 10 per cent range of accuracy. Because of both the current extremely divergent views on climatic effects and also the considerably expanding importance of institutional care for the rheumatic child, our early findings appear to warrant reporting.

Two main factors affected our group of patients: first and probably more important, that of specialized sanitarium care; second, a rather ideal, even, subtropical climatic environment. Our care is comparable to that of most of the larger northern institutions⁶ devoted exclusively to children with rheumatic fever and rheumatic heart disease. Briefly, therapy consists largely of careful medical evaluation, adequate rest, abundant nourishing food, special educational and recreational programs, and salicylates rather conservatively administered where indicated. No sulfonamide prophylaxis is employed. Only northern children with definite, uncomplicated rheumatic heart disease are admitted; and, being a charity institution, those of the lower income brackets. While active cases of rheumatic infection are accepted, a child must be reasonably well to make the trip to Miami. Our data are summarized in Tables I and II.

Only one recurrence was characterized by more than a very slight amount of arthralgia, and that lasted less than one week; one recurrence followed tonsillectomy a month previously; six of the seven cases of recurrence, judged by Jones's⁸ criteria, would have escaped ordinary detection and were found through routine erythrocyte sedimentation rate tests, observation of graphic temperature and pulse charts, along with our perhaps acutely conscious attention to

TABLE I

1. Number of patients with rheumatic heart disease who have been in the National Children's Cardiac Home at least one month, 1936-1945: 88
2. Average year of birth: 1931
3. Average stay: 15.6 months; total patient-years: 114
4. Average cardiothoracic index:
a. On admission: 48.0
b. On discharge: 46.6
5. Active rheumatic fever on admission: 13 cases, or 14.8 per cent.
6. Active rheumatic fever on discharge: 2 cases, or 2.3 per cent
7. Active rheumatic fever recurrences: 7 cases, or 7.9 per cent
8. Improvement on discharge: 86 cases, or 98 per cent

TABLE II. TYPES OF HEART DISEASE

TYPE	NO.	PER CENT
1. All cases of MI	78	89.0
a. MI alone	33	37.5
b. MI plus MS	13	14.8
c. MI plus MS plus AI	19	21.6
d. MI plus AI	10	11.4
2. All cases of MS	35	39.8
a. MS alone	1	1.1
3. All cases of AI	32	36.4
a. AI alone	2	2.3
4. No cases of MS plus AI alone, or of AS		

MI, mitral insufficiency; MS, mitral stenosis; AI, aortic insufficiency; AS, aortic stenosis.

minor symptoms. None followed any detectable respiratory infection, and no discernible precipitating factor was apparent in these cases.

Several instances of very striking improvement occurred, such as functional improvement from a serious aortic insufficiency, considerable decrease in heart size, and general excellent physical improvement. Such instances have also been noted by Dr. Taussig at Baltimore; they deserve only a brief passing word at present.

We have constantly observed about as many cases of colds, bronchitis, virus pneumonia, measles, mumps, and chicken pox as previously seen in clinical experience in the North; severe streptococcus infections were conspicuously rare. Neither scarlet fever nor severe acute tonsillitis was encountered; they appear to be unusual in South Florida. Low-grade streptococcus infections, such as chronic tonsillitis and impetigo, were about as frequent. Throat cultures made nearly once a month the past two years have shown a 10 per cent to 20 per cent incidence of beta hemolytic streptococci the year around. From all this, we surmise streptococcus infection to exist at Miami in a milder form than in the North; and that respiratory infections from other causes are not as capable of inciting an attack of rheumatic fever.

Our experience leads us to believe that a subtropical or tropical climate is more salubrious for the rheumatic fever patient but far from curative. Transporting such patients to a climate such as South Florida should be considered as a prophylactic measure, since fewer and milder recurrences of the disease mean less cardiac damage. Under these circumstances, we are in a position to encourage such an undertaking for the rheumatic patient, but we wish to deplore

attempting to send seriously ill patients over long distances in an attempt to gain small advantage over the active disease. Such effort is, in our experience, misspent and is usually more harmful than good.

With the great economic and social obstacles involved in long transportation, plus home separation, treatment in sanitariums in the South will by no means be the completely satisfactory answer to the rheumatic fever problem. Such will come only from more complete knowledge regarding the pathogenesis of the disease and more effective therapeutic measures during the active phase of the disease. However, as a prophylactic measure, transfer to a subtropical climate may in certain cases be lifesaving and can be highly recommended. The additional change in many instances from poor home environment to good sanitarium care is remarkably beneficial.

SUMMARY

A preliminary report is presented giving our experience with the care of patients with rheumatic heart disease in a subtropical climate amid sanitarium surroundings. The nature of benefit derived from such a climate is primarily prophylactic against repeated and serious recurrences of the disease. Transfer of seriously ill patients with active rheumatic fever is not recommended. The beneficial effect of sanitarium care is stressed.

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RATBITE FEVER

C. G. WATKINS, M.D.
DURHAM, N. C.

RATBITE fever, apparently known in India for 2,300 years, was first reported in the United States by Wilcox¹ in 1840. Since Schottmüller,² in 1914, described a streptothrix as the cause of a case of ratbite fever and Futaki and associates,³ in 1916, demonstrated a spirochete, there has been a great deal of controversy as to which organism was the true etiological agent. However, in recent years both the *Streptothrix muris ratti* (later named the *Streptobacillus moniliformis* by Levaditi and associates⁴ in 1925) and the *Spirochaeta morsus muris* (later renamed the *Spirillum minus* Carter, 1887, by Robertson⁵ in 1924) have been recovered from patients suffering from clinical ratbite fever, and this disease is currently considered to have a dual etiology.* Blake⁶ (1916) reported the first case in the United States caused by the streptobacillus, and Shattuck and Theiler⁷ (1924) reported the first case in the United States caused by the spirillum. Bayne-Jones⁸ presented a brief summary of the first eighty-one cases in the United States from 1840 to 1930. Brown and Nunemaker⁹ reported four additional cases prior to 1931 and forty cases from 1931 to 1940; they also compiled all of the cases occurring in the United States up to 1940 in which the causative organisms were actually demonstrated.

The *Streptobacillus moniliformis* (the name indicates chains of bacilli interspersed with beaded swelling)⁹ is a very pleomorphic, gram-negative, nonacid-fast rod which usually appears straight but occasionally fusiform and varies from 2 to 15 microns in length.¹⁰ Branched forms have been described,^{6, 11, 12} but several recent investigators have not been able to demonstrate true branching.^{9, 13} Brown and Nunemaker⁹ have determined that the basic structure is some sort of "small body," neither a coccus nor a bacillus, which appears linked with other bodies in a chain to produce a segmented filament. These granular filaments have a marked tendency to fragment and therefore do not have uniform length. Large round bodies along the course of the segmented filaments probably contain the viable elements of the culture.

This organism has been identified as the etiological agent not only in ratbite fever, but also in Haverhill fever, which is an epidemic disease, usually milk-borne, but sometimes of unknown source, characterized by petechial rash, arthritis, and septicemia.⁹ Bronchopneumonia caused by this organism has been reported in mice and rats,¹⁴ and therefore the respiratory tracts of these animals probably serve as the sources of this organism at the time of ratbite.

The *Spirillum minus* is an organism which consists of a spiral, short, thick body, 2 to 5 microns in length, with terminal flagella which increase the length to 6 to 10 microns. It is thicker than the *Treponema pallidum* and usually

From the pediatric service of the St. Louis City Hospital.

Presented in part at the meeting of the American Academy of Pediatrics, Nov. 9, 1944, in St. Louis, Mo.

*Henceforth, reference will be made only to the *Streptobacillus moniliformis* and the *Spirillum minus*.

attempting to send seriously ill patients over long distances in an attempt to gain small advantage over the active disease. Such effort is, in our experience, misspent and is usually more harmful than good.

With the great economic and social obstacles involved in long transportation, plus home separation, treatment in sanitariums in the South will by no means be the completely satisfactory answer to the rheumatic fever problem. Such will come only from more complete knowledge regarding the pathogenesis of the disease and more effective therapeutic measures during the active phase of the disease. However, as a prophylactic measure, transfer to a subtropical climate may in certain cases be lifesaving and can be highly recommended. The additional change in many instances from poor home environment to good sanitarium care is remarkably beneficial.

SUMMARY

A preliminary report is presented giving our experience with the care of patients with rheumatic heart disease in a subtropical climate amid sanitarium surroundings. The nature of benefit derived from such a climate is primarily prophylactic against repeated and serious recurrences of the disease. Transfer of seriously ill patients with active rheumatic fever is not recommended. The beneficial effect of sanitarium care is stressed.

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presents one curve per micron, the curves being regular and sharp.¹⁵⁻¹⁸ It moves rapidly across the field of vision by spasmodic spiral movements of the body and whipping, winding, darting movements of the flagella.¹⁵ Excellent photomicrographs of the spirilla have been presented in several reports.¹⁸⁻²⁰

Most cases of this type of infection follow ratbite; however, several cases have been due to other immediate or unknown sources. The best evidence indicates that the source of spirilla at the time of ratbite is the eye discharge produced by the interstitial keratitis and conjunctivitis of the infected rat; this discharge, from which spirilla have been demonstrated, drains into the mouth of the rat.^{16, 21}

It seems timely to introduce several terms for general use. The term "spirillary fever" could be used to include all cases of infection due to the *Spirillum minus*. "Spirillary ratbite fever" could be used as the specific term to indicate ratbite fever due to the *Spirillum minus*. "Streptobacillary fever" could be used as an inclusive term; that is, including those cases associated with ratbite (animal bite) and cases of Haverhill fever. "Streptobacillary ratbite fever" could be used as the specific term to indicate ratbite fever due to the *Streptobacillus moniliformis*.

TABLE I. CHARACTERISTICS OF BOTH TYPES OF RATBITE FEVER

	STREPTOBACILLARY	SPIRILLARY
1. Portal of entry	Animal bite*	Animal bite
2. Incubation period	1 to 22 days (usually less than 10 days)	4 to 28 days (usually more than 10 days)
3. Primary wound	Occasional swelling; usually prompt healing	Prompt healing followed by an indurated ulcer
4. Lymphadenitis	Occasional regional	Frequent regional
5. Fever	Septic, occasional relapsing	Relapsing
6. Rash	Morbilloform; petechial	Roseolar-urticarial (bluish red plaques)
7. Arthritis	Common (70%)	Rare
8. White blood count	10,000-30,000/cu.mm.	5,000-30,000/cu.mm.
9. Serologic tests for syphilis	False positive, 16%	False positive, 51%
10. Complications	Respiratory symptoms; abscesses; endocarditis	Nephritis; endocarditis; herxheimer reaction
11. Mortality	10%, 4 deaths in 39 cases	7%, 3 deaths in 41 cases
12. Therapy	Sodium aurothiomalate; penicillin	Arsenical compounds; penicillin

*Milk-borne infection in Haverhill fever.

A comparison of the two forms of ratbite fever is presented in Table I which is a compilation of the characteristics of the two diseases from several reviews in the past^{8, 9, 22-24} and from a personal review of all reported cases since 1940. The most prominent difference is the frequency of arthritis in streptobacillary infection as contrasted to the very low incidence in spirillary infection. A short incubation period, a septic type of fever, and the presence of petechiae and abscesses point to the probable diagnosis of streptobacillary ratbite fever; whereas, a long incubation period, a relapsing type of fever, and induration and/or ulceration of the primary wound should lead one to suspect a spirillary infection.

Approximately fifty cases of ratbite are seen in the Receiving Room of St. Louis City Hospital each year. During the past eight years, sixteen cases of clinical ratbite fever were seen in the hospital and in six of these cases, the causative organism was demonstrated. Three of the bacteriologically proved cases were seen in 1944 and were of such interest as to warrant being considered in detail.

CASE 14.—E. N. (26849), a 5-month-old white female, admitted to the pediatric service on April 17, 1944, had been bitten by a rat twelve days previously, when her mother had also been bitten by a rat. Her sister had had a rat bite in 1943 but had not become ill.

The patient had been bitten in several places around the mouth (chiefly on the left side of the upper lip) and on the left hand. These were "sore" for a few days, then had healed. The child was apparently well for a week, until the day before admission when her upper lip and left thumb were noted to be swollen. She appeared feverish and ate very little. On the day of entry she became very drowsy and that afternoon had a fever of 102° F.

Examination on admission revealed a well-developed and well-nourished female infant who had a temperature of 100° F. and a papular erythematous rash over the left arm and chest. These papular lesions were solitary, blanched on pressure, varied from 5 mm. to 1 cm. in diameter, totaled twenty to twenty-five in all, and were chiefly on the left arm. There was no regional or general lymphadenopathy. Over the left eye there was a swollen, indurated area where definite bite scars could be seen. The left side of the upper lip was swollen and indurated, and a gray plaque was present in the center of a chancrelike ulcer on the inner surface of the lip. The distal phalanx of the left thumb was swollen on the volar surface; this area was red and fluctuant. A small denuded area was present on the palm. There was no arthritis.

Blood culture, taken on admission, revealed a *Staphylococcus aureus*, which fermented mannite. The blood Kahn and Wassermann tests were negative. The following day the blood count revealed: red cells, 4,060,000 per cubic millimeter; white cells 14,600 per cubic millimeter; and hemoglobin, 9.0 Gm. per cent. Differential white count showed 3 juvenile; 5 stab, and 38 segmented forms; 52 lymphocytes; and 2 monocytes. Urinalysis was negative.

On the day after entry, typical *Spirillum minus* organisms were demonstrated by dark-field examination of the lymph from the chancrelike lesion of the upper lip.* Lymph from this lesion, lymph from the lesion on the left thumb, and blood from the patient were inoculated intraperitoneally into three separate stock mice. Daily dark-field examinations of the peripheral blood of the inoculated mice were negative from the sixth day after inoculation until the ninth day, when *Spirillum minus* organisms were seen in the peripheral blood of the mouse inoculated with the lymph from the lesion on the lip. On the following day, these organisms were also demonstrated in the mouse inoculated with the patient's blood. The mouse inoculated with the lymph from the left thumb was reinoculated seven days later and died in approximately two days. On the day following the second inoculation, dark-field examination of the peripheral blood of this mouse revealed chains of bacilli of varying size; several of these organisms appeared to be branched.

As the infant did not appear to be critically ill, it was decided to observe the expected relapsing temperature course of the disease, and therefore arsenical therapy was postponed. An irregular relapsing temperature course of low grade character was noted during the next week. On the eighth hospital day, the lesions on the lip and thumb were noted to have become worse. The temperature rose to 102.5° F. that evening. Neocarsphenamine (0.0325 Gm., 5 mg. per kilogram) was given intravenously. The temperature continued up to 103.8° F. during the early morning of the following day, when it was noted that the lesions on the lip, left thumb, and above the left eye seemed to be more swollen and

*Demonstrated by Mr. W. H. Gabby, Snodgrass Laboratory, St. Louis City Hospital, St. Louis, Mo.

inflamed. Direct dark-field examination of the lymph from the upper lip was negative approximately eighteen hours after the injection of neoarsphenamine. That evening the patient appeared much improved; the temperature had fallen to 100.5° F. The bluish red color and swelling of the lesions had decreased markedly. The patient vomited occasionally during the first nine days of hospitalization (having lost a total of 600 Gm. in weight) and vomited frequently on the tenth day. Blood Kahn and Wassermann tests had been negative on three different occasions during the hospital stay and both were reported as doubtful on the tenth day. Blood count on this day revealed the following: red cells, 4,800,000 per cubic millimeters; white cells, 32,000 per cubic millimeter; and hemoglobin, 10 Gm. per cent. That evening the patient appeared pale and comatose and began to have short, irregular respirations. Physical examination and a roentgenogram of the chest did not reveal any further positive findings. The patient expired at 8:30 P.M., April 27, 1944.

Autopsy, performed by the coroner's pathologist, revealed no gross abnormalities except slight engorgement of the meningeal vessels. Microscopic findings* revealed diffuse areas of necrosis around the central veins of the liver, slight cloudy swelling of the renal tubular epithelium, and slight engorgement of the meningeal vessels. No Negri bodies, hemorrhages, or areas of encephalitis were noted in the brain sections. There was no evidence of foci of staphylococcal infection. It was thought that these findings were consistent with the pathologic reports of spirillary ratbite fever.

CASE 15.—A. N. (30085) a 29-year-old white woman, the mother of the patient reported in Case 14, was admitted to the surgical service on April 22, 1944. Seventeen days previously she had been bitten by a rat on the right forearm while sleeping. The wound had healed in less than one week but was slightly discolored. There was no redness or tenderness at this time. She had headaches and vertigo eight days after the bite. On the following day, a small, red "pimple" appeared on the bitten area with only slight tenderness. Each day the area seemed to become increasingly red, tender, and swollen. On the day prior to admission, red streaks were noted extending from the bitten area up the arm, and the medial aspect of the elbow became tender. On the morning of admission she applied hot packs to the area which had become black; no other treatment had been attempted.

Examination on admission revealed a well-developed and well-nourished, rational, white female whose temperature was 101.2° F. and pulse was 110. A round, black, necrotic, dry ulcer on the middle of the flexor surface of the right forearm was surrounded by a reddened, warm, indurated area. Scattered red streaks extended from this large area to the elbow and toward the axilla. The right epitrochlear gland was enlarged and tender; however, the right axillary glands were not palpable. A few scattered maculopapules were present on the forehead, cheeks, and neck.

On admission, the blood Kahn and Wassermann tests were negative. The blood count revealed the following: red cells, 4,250,000 per cubic millimeter; white cells, 11,000 per cubic millimeter; and hemoglobin, 12.6 Gm. per cent. The differential count showed 2 eosinophiles; 1 stab; and 62 segmented forms; 31 lymphocytes; and 5 monocytes. Urinalysis of an uncentrifuged specimen was essentially negative except for an occasional pus and/or epithelial cell per low-power field. Admission blood culture was sterile.

The patient's temperature fell to normal on the second day and then continued to be elevated daily between 100.4° F. and 102.2° F. for five days. On the third hospital day, the patient's blood was inoculated intraperitoneally into a mouse; examination of the peripheral blood of this animal was performed daily beginning three days later. On the eleventh hospital day, after the patient had been afebrile for five days and the primary wound had nearly healed, she was inadvertently discharged to the clinic. She returned to the clinic three days later complaining of weakness, nervousness, and increased perspiration and was treated symptomatically. On the following day *Spirillum minus* organisms were found by dark-field examination of the peripheral blood of the inoculated mouse (two weeks after inoculation). Attempts to locate this patient and have her return to the hospital were unsuccessful as she had departed for a visit in Arkansas. She went to see Dr.

*Reported by Dr. K. R. Schlademan, Pathologist, Snodgrass Laboratory, St. Louis City Hospital, St. Louis, Mo.

Valentine Pardo, Monroe, Ark., on May 5, 1944 (four days after last clinic visit), at which time she had red streaks extending up her right arm, temperature of 103° F., generalized rash, and the large ulcer on the right forearm. Sulfathiazole was started in a dosage of 1 Gm. every four hours on May 5, 1944, and continued for two weeks. Neocarsphenamine, 0.6 Gm., was given intravenously on May 14, 1944, and on two later occasions at weekly intervals. Afternoon rise in temperature continued until after the second injection of the arsenical drug. One month later only a small vivid scar remained and the patient had no further complaints.*

CASE 16.—H. L. (2678) a 48-year-old white woman, was admitted to the medical service on Sept. 19, 1944. Fifteen days previously, she had received a ratbite of the left index finger which did not become infected. Five days later her left fifth finger was bitten by a rat; this area became hot, swollen, hard, and red, and remained so for thirty-six hours but gradually subsided without ulceration. On the following day, severe pain was present in the right knee, and two days later, the right ankle became painful. She came to the receiving room on Sept. 13, 1944, at which time she had a swollen right knee, tender wrists, and temperature of 104° F. The patient refused hospitalization on this day and again on the next day when her temperature was 102° F. The right wrist became markedly swollen and tender; the right hip became very painful, so that a change from sitting to standing position was very slow and painful. She had been coughing and had had anorexia since the onset of the illness. A red papular rash was present over her left arm on the day prior to entry. Fever was described as low in the morning and high at night, accompanied by severe night sweats; there had been no chills. She also had had pain and swelling of the right shoulder and elbow. Three of her children were bitten by rats during this period, but none became ill.

Blood Kahn tests on previous admissions in 1936, 1942, and 1943 had been negative.

On admission, physical examination revealed a thin, poorly nourished slightly euphoric, middle-aged white woman who appeared severely ill and who moved slowly because of acute joint pains. There was a fine, scattered, maculopapular, petechial rash over upper and lower extremities; several of the lesions were pustular. The old puncture wounds of the left index finger and hand were almost healed, and there was no lymphadenitis. The right wrist was markedly swollen, tender, hot, and red, with considerable limitation of motion because of pain. The right elbow, shoulder, and hip were very painful on motion but not noticeably swollen. There was slight swelling and tenderness of the right knee. The pharynx was slightly reddened. Scattered wheezes and coarse râles were present generally over both lung fields. The remainder of the examination was negative except for marked varicosities of both lower extremities.

Blood count on admission revealed the following: white cells, 9,700 per cubic millimeter; red cells, 3,480,000 per cubic millimeter; and hemoglobin, 10.7 Gm. per cent. A differential revealed 1 eosinophile; 2 stab and 84 segmented forms; 7 lymphocytes; and 6 monocytes. Urinalysis revealed cloudy urine; specific gravity, 1.021; sugar, negative; and albumin, faint trace. Microscopic examination of voided urine showed 6 to 8 white blood cells per high-power field. Blood Kahn test was positive (3 units), but the Wassermann test was negative.

On the day following admission, the patient's blood was inoculated on special culture media (tryptose meat infusion broth enriched with 20 per cent rabbit serum) and also intraperitoneally into two mice in amounts of 0.3 c.c. and 0.5 c.c. The mouse inoculated with 0.5 c.c. blood died in less than eight hours; death was attributed to the amount of blood inoculated. Frequent dark-field examinations of the peripheral blood of the other mouse did not reveal spirilla during the first three weeks after inoculation. This mouse lived and did not appear ill.

Aspiration of the patient's right wrist joint after the injection of sterile saline resulted in the return of a small amount of slightly cloudy fluid which was inoculated into the previously described special enriched media. A second attempt to aspirate the wrist

*Personal communication with Dr. Valentine Pardo, Monroe, Ark.

joint was made in a similar manner; however, return was clear. This fluid was inoculated intraperitoneally into two mice. Direct dark-field examinations over a three-week period did not reveal spirilla, and the mice did not develop evidence of illness.

Three cultures of the patient's blood on the special enriched media taken on the second and fourth hospital days, and incubated at 37° C. under carbon dioxide tension of approximately 8 to 10 per cent, failed to grow any organisms as did two routine blood cultures on the eighth hospital day. The *Streptobacillus moniliformis* was isolated* from the first joint culture on the second hospital day, and also on the seventh hospital day. This organism was a gram-negative, pleomorphic, chained bacillus in which occasional swollen bodies appeared among the slim bacillary bodies. The characteristic fluff-ball appearance at the bottom of the culture tubes was noted. Growth was slow and the fluff balls did not appear until after forty-eight hours.

The patient had fever during the first ten days, temperature rising to 101.6° F. on the second hospital day and to 102° F. two days later. The petechial rash disappeared on the second day. Roentgenogram of the chest revealed heavy hilar shadows with moderate increase in the peribronchial markings extending throughout both lung fields. A small fibrotic infiltration was observed in the right first interspace. Roentgenograms of the right and left wrist, elbow, shoulder, knee, and ankle joints revealed no abnormality.

Blood drawn for *Streptobacillus moniliformis* agglutination at the end of the first week in the hospital, was sent to the National Institute of Health, Bethesda, Md. Agglutination of the patient's serum against this organism occurred in a titer of 1:160 (agglutination in a dilution of 1:80 or greater is considered diagnostic of infection with this organism⁹).

On the seventh hospital day, when the results of the first joint culture were known, a second joint culture was obtained and the patient was given penicillin in a dosage of 15,000 units subcutaneously every three hours. The second joint culture subsequently grew out the streptobacillus. The next day the patient seemed somewhat improved and complained less of joint pains; however, her right wrist continued to be swollen and markedly tender, and the right knee and hip were slightly tender. Blood Kahn and Wassermann tests were positive, the total Kahn units being 40. Two days after beginning penicillin therapy, all joints seemed to be improving, the right wrist appeared much less swollen but remained tender and almost immobile, and the fever completely subsided. Two days later, the right wrist was only slightly swollen. Penicillin was continued for nine days during which the patient received 1,050,000 units. At this time, she was able to walk with ease, to flex the right wrist, to partially clench the right fist, and very little joint tenderness was present. Blood Kahn test was still positive, but the Wassermann test had become negative. The patient was discharged on Oct. 11, 1944. One month later, blood Kahn and Wassermann tests were negative. Since discharge she has remained afebrile, asymptomatic, and has gained weight during the first five months of 1945.

Table II represents a brief outline of the important clinical findings in each of the sixteen cases of ratbite fever seen in St. Louis City Hospital from 1936 through 1944. In six of these cases, the causative organism has been demonstrated: the *Spirillum minus* in five and the *Streptobacillus moniliformis* in one. Review of this table reveals that four of the sixteen cases occurred in children less than 1 year of age, three in children from 1½ to 4 years, and five later in childhood. In the five proved spirillary infections, incubation periods ranged from eight to twenty-eight days; the primary wound in three cases was inflamed, indurated, and/or ulcerated on admission. The primary wound in the other two cases had been inflamed and swollen but had healed by the time of admission. Regional lymphadenitis was present in three cases, and relapsing fever in all five cases. Blood Kahn tests were positive or doubt-

*Cultured by Mrs. Helen Doubly, Snodgrass Laboratory, St. Louis City Hospital, St. Louis, Mo.

TABLE II. PATIENTS WITH RATBITE FEVER ADMITTED TO ST. LOUIS CITY HOSPITAL.
FROM 1936-1944

CASE	YEAR	AGE (YR.)	INCU- BATION PERIOD (DAYS)	PRIMARY WOUND	RE- GIONAL LYMPH- ADENITIS	TYPE OF FEVER	RASH*	ARTH- RITIS	BLOOD KOH†	BLOOD WASSER- MANN†	ETIOLOG- ICAL AGENT ISOLATED	COURSE†
1 (L. N.)	1936	18	9	Healed	Yes	Relapsing	"Typical"	No	Pos.	Neg.	<i>S. minus</i>	Recovery; nephritis
2 (W. II.)	1936	½2	28	Healed	No	Relapsing	Papulo-vesicular	No	Neg.	0	<i>S. minus</i>	Recovery; splenomegaly
3 (M. E.)	1936	11	2	Necrotic	Yes	Septic	Maculo-papular	No	Neg.	0	None	Recovery
4 (W. P.)	1936	39	7	Indurated; ulcerated	Yes	Relapsing	Maculopapular bullar	No	Neg.	Neg.	None	Relapse; recovery
5 (L. C.)	1936	15	21	Infamed	Yes	Relapsing	Papular	Arth-ralgia	Pos.	A.C.	None	Relapse; recovery
6 (L. S.)	1938	7	16	Infamed	Yes	Irregular; relapsing	None	No	Neg.	0	<i>S. minus</i>	I & D; recovery
7 (G. O.)	1939	8	7	Indurated; ulcerated	Yes	Relapsing	None	No	Pos.	Pos.	None	Recovery
8 (E. R.)	1940	8	14	"Punched-out ulcer"	Yes	Relapsing	R.L.‡	No	Pos.	Pos.	None	Splenomegaly; I & D; recovery
9 (B. D.)	1940	1½	4	Healed	No	Septic	Maculo-papular	No	Neg.	0	None	Recovery
10 (G. W.)	1941	3½	7	Indurated; inflamed	Yes	? (Rapid therapy)	"Typical"	No	Pos.	Pos.	None	Hortheimer; recovery
11 (P. G.)	1942	¾2	13	Indurated; inflamed	No	? (Rapid therapy)	None	No	Neg.	Neg.	None	Recovery
12 (M. H.)	1942	4	13	Indurated; inflamed	Yes	Relapsing	"Typical"	No	Pos.	Doubt.	None	Relapse; recovery
14 (E. N.)	1944	¾2	11	Indurated	No	Relapsing	None	No	Neg.	Neg.	None	Recovery
13 (A. L.)	1942	¾2	21	Indurated; ulcerated	No	Relapsing	Papular	No	Doubt.	Doubt.	<i>S. minus</i>	Autopsy
15 (A. N.)	1944	29	8	Indurated; ulcerated	Yes	Relapsing	Maculo-papular	No	Neg.	Neg.	<i>S. minus</i>	Recovery
16 (H. L.)	1944	48	1-6	Healed	No	Septic	Petechial	Yes	Pos.	Pos.	<i>S. moniliformis</i>	Recovery

* "Typical," bluish red plaques.

† Pos., positive; Neg., negative; Doubt., doubtful; A.C., anticomplementary; 0, not performed.

‡ I & D, incision and drainage.

§ R.L., Red lesions with white centers.

ful in two cases and negative in the other three. In the proved streptobacillary infection, the incubation period was approximately one to six days after two different ratbites. The first wound did not become infected; however, the second wound remained inflamed for thirty-six hours but was healed on admission. There was no lymphadenitis. Septic fever, petechial rash over the extremities, and arthritis of all the major joints of the right side of the body were present. Blood Kahn and Wassermann tests were positive.

Attempts were made to demonstrate the *Spirillum minus* by the mouse inoculation method in fifteen of the sixteen cases. This organism was demonstrated in the five cases by inoculation of the patient's blood into mice and microscopic examination of the peripheral blood of the mice at daily intervals using Gram, Giemsa, or Wright stains and/or dark-field illumination. In Case 1, this organism was demonstrated by Wright's stain in the peripheral blood of a mouse on the twenty-eighth day after inoculation. In Case 6, it was demonstrated on the fifteenth day after inoculation. In Case 15, dark-field examinations of the mouse's blood were unsuccessful daily from the third day until the thirteenth day when *Spirillum minus* organisms were found. In Case 14, the organisms were seen by direct dark-field examination of the lymph of the chancrelike lesion at least nine days prior to the presence of the microorganisms in the peripheral blood of mice inoculated with the patient's blood and lymph from the lesion. This is the first reported case in the United States in which the *Spirillum minus* was demonstrated in the lymph of the primary lesion and then substantiated by finding the organism by the mouse inoculation method. The presence of the streptobacillary organisms in the peripheral blood of the mouse inoculated with lymph from the fluctuant area on the left thumb cannot be adequately explained, because special cultures of the patient's blood for *Streptobacillus moniliformis* were not made. Whether this represents a pre-existing infection of the mouse with this organism or an infection produced by the inoculation of the lymph cannot be determined. This case is the second death due to ratbite fever in which the *Spirillum minus* was demonstrated by present accepted techniques; however, special cultures for *Streptobacillus moniliformis* were not employed in either case. In Case 16, the *Streptobacillus moniliformis* was demonstrated by special culture of joint fluid.

Routine blood cultures were obtained from each of the sixteen patients. The *Streptobacillus moniliformis* was not isolated in any of these cases; however, attempts to culture this organism on special media were made only in Case 16.

Arsenical drugs were used in the treatment of the first fifteen cases, whereas, penicillin was used in Case 16. Nephritis followed an acute exacerbation of spirillary ratbite fever in Case 1, which had been inadequately treated with neoarsphenamine during the first hospital admission. Splenomegaly was present in two cases. Interestingly, incision and drainage were performed in several cases without obtaining pus. A Herxheimer reaction following arsenical therapy occurred in Case 10 and consisted of fever and recurrence of the purplish macular rash.

Two patients (Cases 3 and 9) had very short incubation periods and septic fever. On admission, the wound was necrotic in Case 3 and healed in Case 9. Whether a more extensive bacteriologic study would have been successful in isolating the streptobacillus is impossible to state, but these cases resemble streptobacillary ratbite fever more than any of the other cases of unknown etiology. The other unproved cases resemble spirillary infection in regard to incubation period, wound, induration and/or ulceration, relapsing type of fever, absence of arthritis, and response to arsenicals.

TABLE III. SEROLOGIC TESTS FOR SYPHILIS IN CASES OF RATBITE FEVER

CASE	INTERVAL SINCE BITE (WEEKS)	INTERVAL SINCE ONSET (WEEKS)	KAHN TEST*	KAHN UNITS	WASSER- MANN TEST*
1 (L. N.)†	12	9	4+		-
	20	9	2+		-
5 (L. C.)	3	0	-		0
	5	2	-		0
	7	4	4+		A.C.
	12	9	4+		A.C.
	18	15	1+		-
	19	16	-		0
7 (G. O.)‡	2	1	+		+
	7	6	+		+
	8	7	+		-
8 (E. R.)	8	6	+		-
	9	7	+		+
	65	63	+		-
	90	88	+		-
	108	106	-		-
10 (G. W.)‡	4½	3½	+		+
	5	4	+	160	+
	5½	4½	+	80	+
	6	5	-		-
12 (M. H.)	2	0	-		0
	3	1	-		-
	7	5	+		-
	7½	5½	+		-
	9	7	+		-
	10	8	+		-
	11	9	+	4	-
14 (E. N.)‡	1½	0	-		-
	2	½	-		-
	3	1½	-		-
	3½	2	-		-
16 (H. L.)	2	1	D		D
	3	2	+	3	-
	4	3	+	40	+
	12	11	-	3	-

*Positive, +; Negative, -; Not performed, 0; Doubtful, D; Anticomplementary, A.C.
 †Kahn, negative, twelve weeks prior to bite.
 ‡Mother's serology negative.

From the results of the serological tests for syphilis, in Table III, several interesting facts are apparent. The blood Kahn test is more frequently positive than the Wassermann test, may become positive in as short a period as one week after the onset of ratbite fever, usually becomes positive by the fifth week of the disease (this fact was previously mentioned by Woolley²⁵), and may remain positive for as long as two years after the onset of the illness. A decreasing number of Kahn units was demonstrated in Case 10, following

TABLE IVA. SUMMARY OF ALL CASES OF STREPTOBACILLARY RATBITE FEVER IN THE UNITED STATES

CASE	AUTHOR	YEAR	STATE	AGE (YR.)	DIAGNOSTIC METHOD	S.T.S.*	ARTHRI-TIS	COURSE
1	Blake ⁶	1916	Mass.	67	Blood culture	Neg.	---	Autopsy
2	Litterer ²⁶	1917	Tenn.	14	Blood culture; agglutination	---	---	Recovery
3	Litterer ²⁶	1917	Tenn.	5	Blood culture; agglutination	---	---	Recovery
4	Dick and Tunnicliff ²⁷	1918	Ill.	10	Blood culture	Pos. (syphilis)	---	Recovery
5	Tunnicliff ¹¹ and Mayer	1918	Ill.	$\frac{1}{32}$	Blood culture	Neg.	---	Autopsy
6	Dodd ²⁸	1926	Md.	10	Blood culture	Neg.	Yes	Recovery
7	Hazard and Goodkind ²⁹	1932	Mass.	58	Blood culture	---	Yes	Recovery
8	Scharles and Seastone ¹⁰	1934	Mass.	Adult	Culture of joint fluid; agglutination	---	Yes	Recovery
9	Dawson and Hobby ³⁰	1939	N. Y.	Adult	Skin and blood culture	Pos.	Yes	Recovery
10	Dawson and Hobby ³⁰	1939	N. Y.	Adult	Blood culture	Pos.	Yes	Recovery
11	Farrell and associates ¹²	1939	N. Y.	40	Blood culture	Neg.	Yes	Recovery
12	Allbritten and associates ²³	1940	Pa.	21	Blood culture	Neg.	Yes	Recovery
13	Hart ²²	1941	Va.	18	Agglutination; animal inoculation and culture	---	Yes	Recovery
14	Larson ³¹	1941	D. C.	$\frac{7}{12}$	Blood culture	---	No	Recovery
15	Larson, ³¹ Brown and Nunemaker ⁹	1941	D. C.	21	Agglutination	Pos.	Yes	Recovery
16	Beach and Ravenel ³²	1941	S. C.	$\frac{1}{12}$	Agglutination	Neg.	Yes	Recovery
17	Brown and Nunemaker ⁹	1942	Md.	49	Blood culture; agglutination; joint fluid culture	Neg.	Yes	Recovery
18	Brown and Nunemaker ⁹	1942	Md.	$\frac{2}{12}$	Blood culture; agglutination	Doubtful	No	Recovery
19	Brown and Nunemaker ⁹	1942	Md.	$\frac{1}{12}$	Abscess culture; agglutination; blood culture; animal inoculation	Neg.	Yes	Recovery
20	Brown and Nunemaker ⁹	1942	Md.	$\frac{10}{12}$	Agglutination	Neg.	No	Recovery
21	Brown and Nunemaker ⁹	1942	Md.	$\frac{1}{12}$	Agglutination	Doubtful	No	Recovery
22	Brown and Nunemaker ⁹	1942	Md.	$\frac{2}{12}$	Agglutination	Neg.	Yes	Recovery
23	Brown and Nunemaker ⁹	1942	Md.	$\frac{4}{12}$	Agglutination	Neg.	Yes	Recovery
24	Witzberger and Cohen ²⁴	1944	N. Y.	$\frac{3}{12}$	Blood culture	Neg.	No	Recovery
25	Blake and associates ³³	1944	Conn.	73	Blood culture	---	Yes	Autopsy
26	Heilmán and Herrell ³⁴	1944	Minn.	47	Blood culture	---	---	Recovery
27	Buddingh ³⁵	1944	Tenn.	59	Blood and joint fluid cultures; chick embryo inoculation	---	Yes	Recovery
28	Robins ³⁶	1944	Ky.	70	Blood culture; abscess culture	Neg.	No	Recovery
29	Rosen and Denzer ³⁷	1944	N. Y.	$\frac{9}{12}$	Blood culture; animal inoculation	Neg.	No	Recovery
30	Altmeier and associates ³⁸	1945	Ohio	$\frac{3}{12}$	Blood culture	---	Yes	Recovery
31	Altmeier and associates ³⁸	1945	Ohio	$\frac{10}{12}$	Blood culture	Neg.	No	Recovery

*Serological test for syphilis.

--- Not mentioned.

TABLE IVA.—CONT'D

CASE	AUTHOR	YEAR	STATE	AGE (YR.)	DIAGNOSTIC METHOD	S.T.S.*	ARTHRITIS	COURSE
32	Altemeier and associates ³⁸	1945	Ohio	$\frac{2}{12}$	Blood culture	Neg.	No	Recovery
33	Altemeier and associates ³⁸	1945	Ohio	$4\frac{1}{2}$	Blood culture	Neg.	Yes	Recovery
34	Wheeler ³⁹	1945	Mich.	Inf.	Blood culture	---	---	Death
35	Wheeler ³⁹	1945	Mich.	$\frac{2}{12}$	Blood culture	Neg.	Yes	Recovery
36	Wheeler ³⁹	1945	Mich.	$\frac{1}{12}$	Blood culture; abscess culture	---	Yes	Recovery
37	Wheeler ³⁹	1945	Mich.	$\frac{9}{12}$	Blood culture; mouse inoculation	Neg.	No	Recovery
38	Wheeler ³⁹	1945	Mich.	$1\frac{2}{12}$	Blood culture	---	---	Recovery
39	Watkins	1945	Mo.	48	Joint culture; agglutination	Pos.	Yes	Recovery

nearsphenamine therapy. An increasing number of Kahn units was demonstrated in Case 16, followed by a decreasing number following penicillin therapy.

Since Blake (1916)⁶ reported the first streptobacillary case and Shattuck and Theiler (1924)⁷ reported the first spirillary case in the United States, there have been a rapidly increasing number of bacteriologically proved cases. In Tables IVA and IVB, proved cases in the United States are presented according to the diagnostic method used, serology, subsequent course, and in the streptobacillary cases, the presence or absence of arthritis.

There have been thirty-nine proved cases of streptobacillary ratbite fever reported in the United States from 1916 through the first six months of 1945. Thirty-seven of these cases followed ratbite, one followed weasel-bite,²⁷ and the other followed trauma.²⁹ The streptobacillus was isolated from the blood cultures of thirty patients, two of whom had positive joint cultures,^{9, 35} one had positive skin culture,³⁰ three had positive abscess cultures,^{9, 36, 39} five had positive agglutinations,^{9, 26} and three had positive animal inoculations.^{9, 37, 39} Two cases, one reported by Scharles and Seastone,¹⁰ and the streptobacillary case of the present series, were proved by positive joint fluid cultures and agglutinations. One case was proved by agglutination, animal inoculation, and blood culture of the animal.²² The remaining six cases were established by agglutination alone.^{9, 31, 32} Tileston⁵² described a streptothrix present on direct dark-field examination and direct stain of the patient's blood; however, this case has not been included among the thirty-nine cases as there was no further positive bacteriologic data.

There have been forty-one bacteriologically proved cases of spirillary ratbite fever reported in the United States from 1924 through the first six months of 1945. Thirty-three cases followed ratbite, one followed mouse-bite,⁴⁹ two followed contact with dogs in a laboratory,²⁰ one followed cat-bite,⁴⁷ one followed cat-scratch,⁵³ one followed trauma to the knee without known animal contact,⁵³ in one there was no history of ratbite but the patient had been in a rat-infested area,⁶¹ and one, although there was no history of ratbite, animal contact, or trauma, was diagnosed by the relapsing type of fever and by ani-

TABLE IVB. SUMMARY OF ALL CASES OF SPIRILLARY RATBITE FEVER IN THE UNITED STATES

CASE	AUTHOR	YEAR	STATE	AGE (YR.)	DIAGNOSTIC METHOD	S.T.S.*	COURSE
1	Shattuck and Theiler ⁷	1924	Mass.	3½	Blood inoculation into mouse and guinea pig	Neg.	Recovery
2	Dembo and associates ⁴⁰	1925	Ohio	7½	Direct dark-field of lymph (wound)	Neg.	Recovery
3	Lawson and Lanford ⁴¹	1925	La.	Child	Lymph into mice	---	Recovery
4	Ward ⁴²	1926	N. C.	3½	Direct dark-field of lymph (gland)	Pos.	Recovery
5	Zahorsky ⁴³	1926	Mo.	--	Direct dark-field of lymph (wound)	---	Recovery
6	Bayne-Jones ⁴⁴	1927	N. Y.	48	Skin biopsy into guinea pig	Pos.	Recovery
7	Leadingham ⁴⁵	1928	Ga.	20	Blood into mice	---	Recovery
8	Leadingham ⁴⁵	1928	Ga.	11	Blood into mice	Pos.	Recovery
9	Francis ⁴⁶	1932	Va.	6	Gland lymph into white rat	---	Recovery
10	Mock and Morrow ⁴⁷	1932	Ill.	43	Blood into guinea pig	Pos.	Recovery
11	Ripley and Van Sant ²⁰	1934	Ill.	26	Blood into mice, guinea pigs, and dogs	Pos.	Recovery
12	Ripley and Van Sant ²⁰	1934	Ill.	22	Blood into mice, guinea pigs, and dogs	Pos.	Recovery
13	Koerber ⁴⁸			12	Gland into rat; blood into guinea pig	---	Recovery
14	Reitzel and associates ⁴⁹	1936	Calif.	14	Gland and blood into mice	Neg.	Recovery
15	Woolley ⁵⁰	1936	Mass. Calif.	6½	Gland and blood into guinea pigs	Pos.	Recovery
16	Marshall ⁵¹	1936	Ky.	2	Direct stain of lymph (wound)	Pos.	Recovery
17	Bloch and Baldock ⁵²	1936	Ky.	3	Blood into mice	Pos.	Recovery
18	Walker ⁵³	1937	Va.	16	Blood into guinea pig	Neg.	Recovery
19	Walker ⁵³	1937	Va.	50	Blood into guinea pig	Neg.	Recovery
20	Leadingham ⁵⁴	1938	Ga.	7	Blood into mice	Neg.	Recovery
21	Gilkey and Dennie ⁵⁵	1939	Mo.	5	Direct dark-field on lymph (wound)	Pos.	Recovery
22	Gilkey and Dennie ⁵⁵	1939	Mo.	3	Gland lymph into mouse	Neg.	Recovery
23	Woolley ²⁵	1939	Mass.	3½	Blood into guinea pig	Pos.	Recovery
24	Woolley ²⁵	1940	Oreg.	6	Lymph into guinea pig	Pos.	Recovery
25	Greengard and Hess ⁵⁶	1941	Ill.	1½	Blood into mice	Pos.	Autopsy
26	Packchianian and Sweet ⁵⁷	1941	D. C.	½	Blood into mice and guinea pigs	Neg.	Recovery
27	Larson ⁵¹	1941	D. C.	3½	Blood into white rats†	Neg.	Recovery
28	Rogliano ⁵⁸	1942	N. Y.	4½	Blood into mice	Neg.	Recovery
29	Rogliano ⁵⁸	1942	N. Y.	13	Direct smear of blood; blood into mouse	Pos.	Recovery
30	Burk and Hodas ⁵⁹	1943	N. Y.	65	Direct dark-field of lymph (wound)†	Neg.	Recovery
31	Beeson ⁶⁰	1943	Ga.		Blood into mice†	Pos.	Recovery
32	Beeson ⁶⁰	1943	Ga.	2	Blood into mice†	Neg.	Recovery
33	Witzberger and Cohen ²⁴	1944	N. Y.	59 3½	Blood into mice and rats†	Pos.	Recovery

TABLE IVB.—CONT'D

CASE	AUTHOR	YEAR	STATE	AGE (YR.)	DIAGNOSTIC METHOD	S.T.S.*	COURSE
34	Heilmann and Herrell ³⁴	1914	Minn.	7	Blood into mice	---	Recovered; arsenic; encephalitis
35	Hitzig and Liebesman ⁶¹	1944	N. Y.	23	Special blood culture	Pos.	Autopsy
36	Wheeler ³⁹	1945	Mich.	3½	Blood into mice†	Neg.	Recovery
37	Watkins	1945	Mo.	18	Blood into mice	Pos.	Recovery
38	Watkins	1945	Mo.	4½	Blood into mice	Neg.	Recovery
39	Watkins	1945	Mo.	7	Blood into mice	Neg.	Recovery
40	Watkins	1945	Mo.	5½	Mouse inoculation and dark-field of lymph (wound)	Doubt.	Autopsy
41	Watkins	1945	Mo.	29	Blood into mice	Neg.	Recovery

*Serological test for syphilis.

†Agglutination (*Streptobacillus moniliformis*) negative.

‡Blood culture negative for *Streptobacillus moniliformis*.

— Not mentioned.

mal inoculation of lymph gland.⁴⁶ Twenty-nine cases were established by animal inoculation of patient's blood, including the first six cases mentioned, not following ratbite. In the case with no history of ratbite in which the patient had lived in rat-infested areas, *S. minus* organisms were cultured by a special technique discussed later.⁶¹ Rogliano⁵⁸ reported a diagnosis established by direct stain of the patient's blood and confirmed by animal inoculation. Four cases were diagnosed by direct dark-field examination of the lymph from the primary wound,^{40, 42, 55, 59} one case was diagnosed similarly by examination of the lymph from a lymph node,⁴² and one case was diagnosed by direct stain of the lymph from the wound.⁵¹ These cases were not confirmed by animal inoculation. Case 14 of the present series was diagnosed by direct dark-field examination of the lymph from the wound, and this finding was confirmed by mouse inoculation. Three cases were established by animal inoculation of lymph gland material.^{46, 48, 55} Another case was established by inoculating the material of a skin biopsy into guinea pigs and demonstrating the spirilla in the peripheral blood of the animals.⁴⁴

Arthritis was present in twenty-one of the thirty-one cases of the streptobacillary form in which the presence or absence of arthritis was mentioned, representing 68 per cent. Walker⁵³ reported a case of the spirillary form in which there was arthritis, this being the only such case reported in the United States. Joint pains were present in another case, but there was no definite arthritis.⁵⁹

There have been four deaths reported due to streptobacillary ratbite fever in the United States and the autopsy findings have been described in three of these cases. Blake⁶ reported the first case in which the pathologic findings were: ulcerative endocarditis due to streptothrix (now considered the streptobacillus), subacute myocarditis, and subacute glomerular and interstitial nephritis. The second case was reported by Tunnicliff and Mayer,¹² in which there were the following pathologic findings: pallor of the viscera, broncho-

pneumonia, suprarenal hemorrhages, and hyperemia of the liver. Blake, Horstmann, and Arnold³³ in 1944, reported a case in which the anatomic diagnoses were as follows: focal myocarditis and pneumonia, and fibrous pleural and peritoneal adhesions. Wheeler³⁹ mentioned a case diagnosed by blood culture in which the child died of diarrhea and jaundice after having had one dose of mapharsen. No autopsy findings were mentioned. Brown and Nunemaker⁹ called attention to two streptobacillary infections which had not been reported: Dr. Ruben Schulz of Boston performed the autopsy in the first case, in which the patient had endocarditis; in the second case, a patient of Dr. L. A. Krause of Baltimore, had a myocardial abscess. Sources of these infections were not mentioned.

There have been very few pathologic reports of spirillary ratbite fever. The pathologic findings in Case 14 of the present series were chiefly, central necrosis of the liver, cloudy swelling of the tubular epithelium of the kidneys, and slight engorgement of the meningeal vessels. Greengard and Hess⁵⁶ reported the clinical and pathologic summary of a 23-day-old child who developed ratbite fever and died approximately three weeks later. The *Spirillum minus* was demonstrated by the mouse inoculation method. Anatomic diagnoses were: bilateral hemorrhagic bronchopneumonia, acute serosanguineous tracheobronchitis, serofibrinous pericarditis, hemorrhagic nephritis, cloudy swelling of the myocardium, liver, and kidneys, and septic hyperplasia of the spleen. Brown and Nunemaker⁹ questioned the etiology of the bronchopneumonia, and the acceptance of the spirillum as the cause of the ratbite fever since there had been no mention of the streptobacillus or streptothrix. In view of the pathologic findings, this might well represent a case of mixed streptobacillary-spirillary ratbite fever. As no attempt to culture for streptobacillus was made in Case 14 of the present series, the presence of a mixed streptobacillary-spirillary infection also cannot be excluded. Hitzig and Liebesman⁶¹ described a case of proved spirillary infection in which an adult with no history of ratbite had positive blood Kahn and Wassermann tests, blowing systolic apical murmur, high-pitched diastolic murmur at the left of the sternum in the third intercostal space, and evidence of peripheral embolism. Repeated cultures by special technique revealed an organism resembling *Spirillum minus* in many details. Anatomic diagnoses were as follows: Subacute endocarditis of the mitral and aortic valves due to spirillum, rheumatic heart disease (chronic interstitial valvulitis of mitral and aortic valves, rheumatic myocarditis), infectious splenitis, splenomegaly, subacute splenic infarct, pulmonary congestion and edema, and chronic passive congestion of the liver. Autopsy findings of two cases reported by Japanese investigators⁴⁷ revealed the following parenchymatous changes in the organs: marked hyperemia, swelling, and degeneration of the tubular epithelium of the kidneys; degeneration, necrosis, and destruction of liver cells, particularly in the acinus centers with hyperemia and hemorrhages. There was a generalized hyperemia of the organs including the kidneys, liver, and meninges of the brain which were also edematous.

It is interesting in reviewing Table V that ratbite fever has occurred in thirty-one states and the District of Columbia, that spirillary cases have been

TABLE V. DISTRIBUTION OF RATBITE FEVER IN THE UNITED STATES

STATE	TOTAL NO. OF CASES*	PROVED CASES DUE TO S. MONIL- IFORMIS	PROVED CASES DUE TO S. MINUS	STATE	TOTAL NO. OF CASES	PROVED CASES DUE TO S. MONIL- IFORMIS	PROVED CASES DUE TO S. MINUS
1. Ala.	1	--	--	17. Neb.	2	--	--
2. Calif.	4	--	2	18. N. J.	1	--	--
3. Conn.	4	1	--	19. N. Y.	18	5	6
4. Ga.	8	--	5	20. N. C.	1	--	1
5. Ill.	17	2	4	21. N. D.	1	--	--
6. Ind.	4	--	--	22. Ohio	20	4	1
7. Iowa	4	--	--	23. Okla.	2	--	--
8. Kan.	1	--	--	24. Ore.	1	--	1
9. Ky.	6	1	2	25. Pa.	10	1	--
10. La.	6	--	1	26. S. C.	6	1	--
11. Md.	8	8	--	27. Tenn.	4	3	--
12. Mass.	6	3	3	28. Texas	2	--	--
13. Mich.	6	5	1	29. Va.	4	1	3
14. Minn.	2	1	1	30. W. Va.	5	--	--
15. Miss.	2	--	--	31. Wis.	1	--	--
16. Mo.t	22	1	8	D. C.	5	2	2
Total					184	39	41

*Total number includes proved and unproved cases.

†Including cases reported in this paper.

reported in all regions of the United States, but that there have been as yet no reported streptobacillary cases west of Minnesota and Missouri. Foncannon⁶³ reported a case in Kansas in which the *Spirillum minus* was isolated by blood culture. As no further bacteriologic data were mentioned, this case was not considered a proved case in a previous review of the literature.⁹

Excellent reviews of the various diagnostic methods of isolating both organisms have been previously presented by Brown and Nunemaker,⁹ and Witzberger and Cohen.²⁴ Chief methods of demonstrating the *Streptobacillus moniliformis*⁹ as the causative organism are as follows:

1. Blood cultures

- Use of enriched media, such as tryptose phosphate and dextrose starch broth and agar enriched with 20 per cent serum (horse, rabbit, beef) or ascitic fluid
 - Use of tubes with 5 to 6 c.c. of media
 - Culture of the centrifugate of citrated blood
 - Rapid transfer; i.e., subculture within twenty-four hours
- Joint and abscess cultures as mentioned
 - Agglutination: titer of 1:80 or above, indicative of infection
 - Skin test with specially prepared streptobacillary antigen, producing a 1 to 3 cm. reaction when positive
 - Mouse inoculation: virulent for mice early
 - Inoculation into chick embryo, producing arthritis

Buddingh³⁵ recently reported on the culture by the last method and found evidence suggesting that in the initial stages, the microorganisms behaved as facultative intracellular parasites within the cytoplasm of the synovial cells.

Wheeler²⁹ has suggested a slightly easier culture method; i.e., inoculation of at least 8 c.c. of blood to 50 c.c. of broth routinely employed, and subculture

unsuccessfully, having had positive cultures of the blood, bite abscesses, and secondary abscess of the leg. This patient was given 30,000 units of penicillin intravenously every morning and 15,000 units intramuscularly every three hours for three days, then 67,500 units every twenty-four hours. Five days later, fever returned, and the patient was started on the initial doses. An afebrile course followed. Total dosage of penicillin was 1,922,000 units. Arthritis had not been present. In a preliminary report of a case in Great Britain, Kane⁶⁵ described the course of a 15-year-old patient with ratbite fever treated late with penicillin. On the fiftieth day of the patient's illness, the *Streptobacillus moniliformis* isolated previously from blood culture, was found to be penicillin sensitive. After receiving 200,000 units of penicillin administered in forty-eight hours, the patient became afebrile and remained so thereafter. Altemeier and associates,³⁸ reported three cases of streptobacillary ratbite fever treated with penicillin. In the first case, a 10-month-old female was treated for one day with sulfathiazole; after a blood culture was positive for the streptobacillus, she was given 12,500 units of sodium penicillin intravenously every four hours for two and one-half days, then 5,000 units intramuscularly for six days, for a total of 302,500 units during eight and one-half days. Rapid recovery was noted by the disappearance of septicemia and fever. Arthritis had not been present. In the second case, a 2-month-old male had positive blood cultures on admission, but no arthritis. Penicillin was given on the third hospital day in amounts of 12,500 units intravenously or intramuscularly every four hours for the first two days, for a total of 212,500 units over four and one-half days; blood cultures became negative, patient became and remained afebrile after the third day of therapy. In the third case, a 4½-year-old female had arthritis and positive blood cultures; 4,000 units of penicillin were given intravenously every four hours for three days, then intramuscularly for two more days, 132,000 units only being available. Blood cultures became negative, rash and arthritis subsided two and five days, respectively. Recurrence occurred four days after cessation of therapy; that is, fever, rash, and positive blood cultures were present; recovery was complete two weeks later. From experience in these three cases, Altemeier and associates,³⁸ recommended the use of 10,000 to 15,000 units every three hours for seven days.

Wheeler³⁹ reported four infants with proved streptobacillary ratbite fever treated successfully with penicillin in amounts of 5,000 units every two hours. In the first case, a 7-week-old baby had arthritis of the ankles and wrists and septic fever; fever disappeared after the second day and arthritis after the fifth day of penicillin therapy. In the second case, a 5-week-old premature infant had tracheobronchitis, sternal abscess, and arthritis of tarsal-metatarsal joints which disappeared after five to seven days of penicillin therapy. In the third case, a 6-month-old Negro infant had septic fever, marked irritability, and opisthotonos; these symptoms disappeared after four to five days of penicillin therapy. In the fourth case, a 14-month-old child had fever, rash, and irritability which disappeared on the second day of penicillin therapy.

In Case 16 of the present series, 15,000 units of penicillin were given subcutaneously every three hours for a total of 1,050,000 units; the patient had an excellent recovery from a severe arthritis.

Wheeler³⁹ also reported the first patient with spirillary ratbite fever treated with penicillin. In this case, a 3-month-old Negro boy had high fever, a coarse macular rash over the chest, and red indurated areas on the face and scalp. Blood cultures did not grow the *Streptobacillus moniliformis*; however, *Spirillum minus* was demonstrated by the mouse inoculation method. Penicillin was administered intramuscularly in amounts of 5,000 units every three hours. Fever disappeared in less than twelve hours after penicillin therapy, and the patient was asymptomatic following five days of therapy.

These clinical reports very conclusively establish penicillin as the drug of choice in the treatment of ratbite fever. Undoubtedly some of the deaths from both types of ratbite fever could be avoided by the early use of penicillin.

SUMMARY AND CONCLUSIONS

1. Sixteen cases of ratbite fever, treated in the St. Louis City Hospital during the period from 1936 to 1944, are presented.
2. The etiological agent was demonstrated in six cases, five being due to the *Spirillum minus* and one being due to the *Streptobacillus moniliformis*.
3. The first case of ratbite fever in the United States has been reported in which the *Spirillum minus* was demonstrated in the lymph of the primary wound by direct dark-field examination and demonstrated later by mouse inoculation methods.
4. Autopsy findings of this case due to the *Spirillum minus* are presented.
5. A case of ratbite fever due to the *Streptobacillus moniliformis* successfully treated with penicillin has been presented.
6. A review of the literature has been made with regard to the symptomatology, mortality, pathology, diagnostic methods, geographical incidence, and the therapy of both types of ratbite fever.
7. Penicillin is indicated early in the treatment of either type of ratbite fever after correct diagnostic procedures have been employed.

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THE PREPARATION AND USE OF CONCENTRATED RED BLOOD CELL TRANSFUSIONS IN INFANCY

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DURING the last few years, whole blood transfusions of fresh blood have been largely replaced in our hospital by preserved blood because of its availability.

The preparation of bank blood sometimes requires dilution. This enhances, to a degree, its use in conditions associated with any degree of hemoconcentration. However, it is at a distinct disadvantage in the very young infant and child because repeated transfusions are difficult to administer. It is at a disadvantage where one is dealing with hemolytic anemias, both acute and chronic. In order to combat these objections, we have concentrated bank blood at the time of use and have administered such blood concentrated to an even greater cell count than that of whole blood, with satisfactory results.

Pediatric patients because of their size are limited as to the volume of fluids that can be administered at any one time. In some instances the accessibility of venipunctures is an important limiting factor. Here the value of concentrated cell transfusion is obvious. Favorable results with blood concentrates on adult patients have been published by different workers who vary slightly in their method of concentrating the blood. Watson,¹ Williams and Davie,² and Goodall³ have simply removed the plasma either leaving the middle layer of "gel" of white blood cells and fibrin or taking measures to exclude that layer. Murray and associates,⁴ McQuaide and Mollison,⁵ and Alt⁶ have added solutions of either saline or glucose-saline apparently to reduce the viscosity of the cells, facilitating administration. The resultant concentrates are reported as having red blood cell counts of six million to eight million per cubic millimeter and hemoglobin content of from 17 to 20 Gm. per 100 c.c. We have concentrated red blood cells from "bank blood" which are prepared according to the method of Muether and Andrews,⁷ using dextrose-citrate-buffer solution. With this, it is necessary simply to siphon off the supernatant fluid. It has been found⁸ that the "gel" layer does not form in sufficient amount to require removal and the resultant concentrate has been given without any difficulty with the usual methods of intravenous administration.

PROCEDURE

Bank blood, preferably that which has been of recent preparation, is removed without shaking from the cooler. A needle is inserted in the rubber top and attached to a siphon apparatus. A second needle is placed in the top, connecting the upper part of the bottle with the outside air. The first needle is long enough to reach down to the cell layer. The supernatant fluid is then

siphoned off. Approximately 600 c.c. is removed from the bank blood mixture. That which remains in the bottle now contains a count of approximately seven to eight million red blood cells per cubic millimeter. This is then used in a routine manner of administration to the patient.

This type of blood has been administered satisfactorily without complication in ten cases of erythroblastosis fetalis, repeatedly in two cases of Cooley's anemia, repeatedly in two cases of acute hemorrhagic nephritis, in anemia of the premature infant, and in a case of cord hemorrhage and one of hemorrhage from the penis in newborn infants, which, including adults, totals 150 cases without mishap.

ADVANTAGES

Advantages of this procedure are:

1. Availability.
2. Method of preparation associated with minimum risk of contamination.
3. Minimum equipment required.
4. High cell volume, where cells are eventually needed, particularly in the newborn.

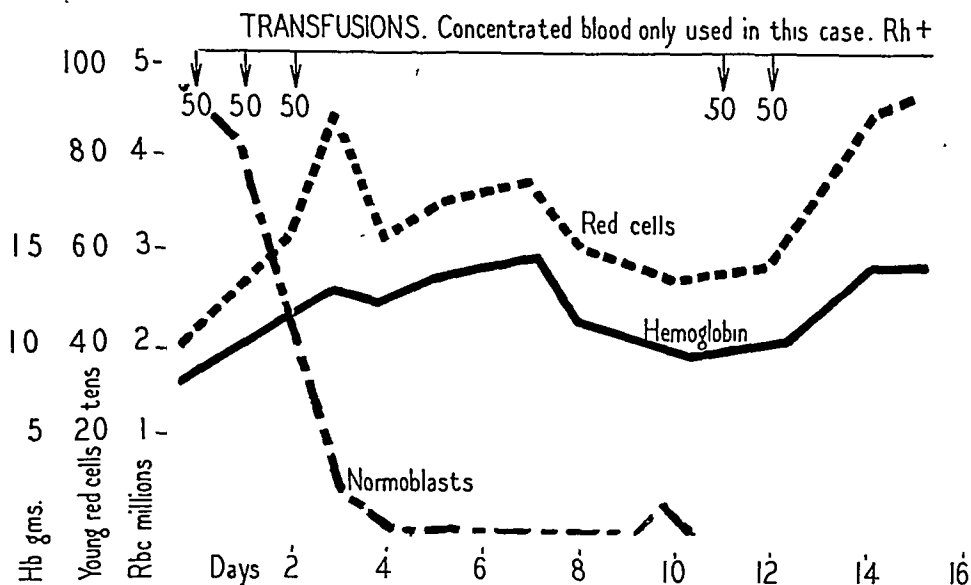


Fig. 1.

EXEMPLARY CASES

Erythroblastosis Fetalis.—The child was born jaundiced. The total white blood count twelve hours after delivery was 20,000; the total red blood count was 3,800,000. Examination of the Wright's stained blood smear showed 60 erythroblasts per 100 white blood cells counted. Mother was Rh-negative; baby was Rh-positive. Physical examination was negative except for noted icterus, splenomegaly, and hepatomegaly. Concentrated bank blood, 75 c.c., Rh-positive, was administered. Twelve hours later, the white blood count was 10,000; erythroblasts, 25 per 100 white blood cells; red blood count, 4,000,000. Twelve hours later 50 c.c. of concentrated bank blood was administered. Twelve hours later the white blood count was 9,000; erythroblasts, 10 per 100 white blood cells counted; red blood count,

4,200,000. The jaundice was at a standstill; icteric index, 100 units. Twenty-four hours later icteric index, 50; white blood count, 10,000; erythroblasts, 3 per 100 white blood cells; red blood count, 4,200,000. Three days hence there was no apparent jaundice to the naked eye; the white blood count was 9,000; erythroblasts, none seen; red blood count, 4,100,000; Weight gain was satisfactory. Result: complete regression of erythroblastosis fetalis (Fig. 1).

Cooley's Anemia.—M. S., aged 7 months, entered the hospital Sept. 1, 1943, with pallor, weakness, and vomiting of two weeks' duration. During this period she showed no weight gain. There was no diarrhea. Physical examination revealed hepatomegaly and splenomegaly. The patient was one of twins. Sibling twin died at 6 weeks. Birth history was normal. The infant was breast fed until onset of illness two weeks previously, when she was put on evaporated milk. Family history, Italian parentage. Patient had a cousin with Cooley's type of anemia which had not been benefited by a splenectomy. All relatives were dark, olive-skinned people who looked pale.

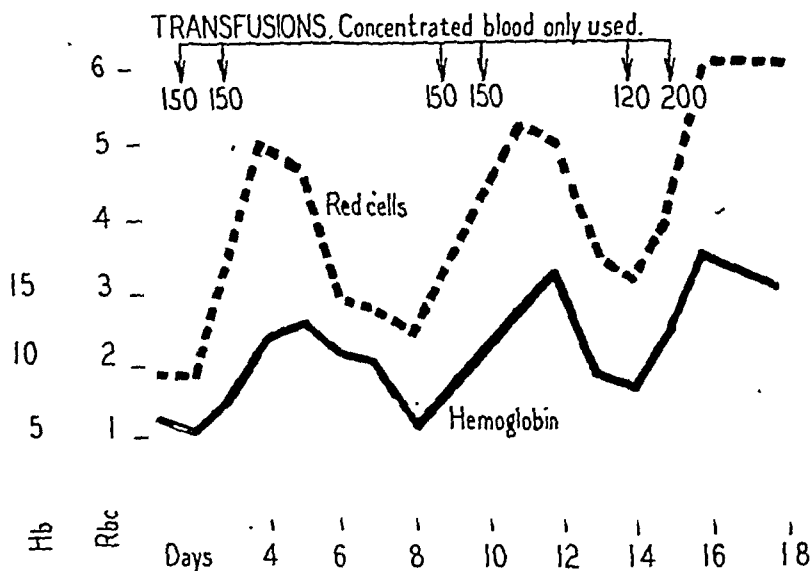


Fig. 2.

Laboratory Data and Progress.—The initial red blood count was 1,870,000; hemoglobin, 6.0 Gm.; white blood count, 21,000; normoblasts, 18 per 100 white blood cells on Wright's stained blood smear; hematocrit, 16 volume per cent; cell fragility test with saline, 0.38 to 0.22; mean corpuscular volume, 89.5; mean corpuscular hemoglobin, 33; mean corpuscular hemoglobin concentration, 37 per cent. Study of stained smear revealed polychromatophilia, achromia, anisocytosis, and poikilocytosis. Concentrated cells, 150 c.c., were given two days after the laboratory work was done. Following this, the red blood cell count was 3,370,000; hemoglobin, 8.0 Gm.; hematocrit, 22 volume per cent; normoblasts, 11 per cent. On the third day, 150 c.c. of concentrated cells were given. Following this, the red blood count was 5,100,000; hemoglobin, 12.0 Gm.; hematocrit, 32 volume per cent. By the twelfth day, the red blood count had gradually fallen to 2,650,000; hemoglobin, 6.0 Gm.; normoblasts, 6 per cent. Concentrated blood, 150 c.c., was given the thirteenth and fourteenth days. Following this, the red blood count was 5,580,000; hemoglobin, 15.0 Gm. On the eighteenth day, the red blood count had dropped to 3,260,000. Concentrated blood, 150 c.c., again was given daily for two days. Following this, the red blood count rose to 6,130,000; hemoglobin, 15.0 Gm. Patient was discharged. Since then, the patient has been in and out of the hospital for transfusions. Anemia invariably has returned over varying periods of time. Thus far, the response to transfusion has been only transitory (Fig. 2).

Anemia of the Premature.—The patient, a boy, was one of twins. Premature birth occurred at six months' gestation. Birth weight was 2 pounds, 11 ounces. Delivery was not difficult. The respiration and cry were spontaneous though sluggish. He was put on Olac formula and did well for one and one-half months. He then developed pallor and his weight gain became less progressive. The red blood count was 2,800,000; hemoglobin, 9.0 Gm. The patient was transfused with concentrated cells, 30 c.c., on two successive days. The red blood count rose to 5,500,000; hemoglobin, 14.0 Gm. The patient's color improved and weight gain became normal. Eight months later the baby showed continued weight gain, and the red cell count was 4,200,000 with a hemoglobin of 10.0 grams. Follow-up revealed no anemia; no transfusion reactions (Fig. 3).

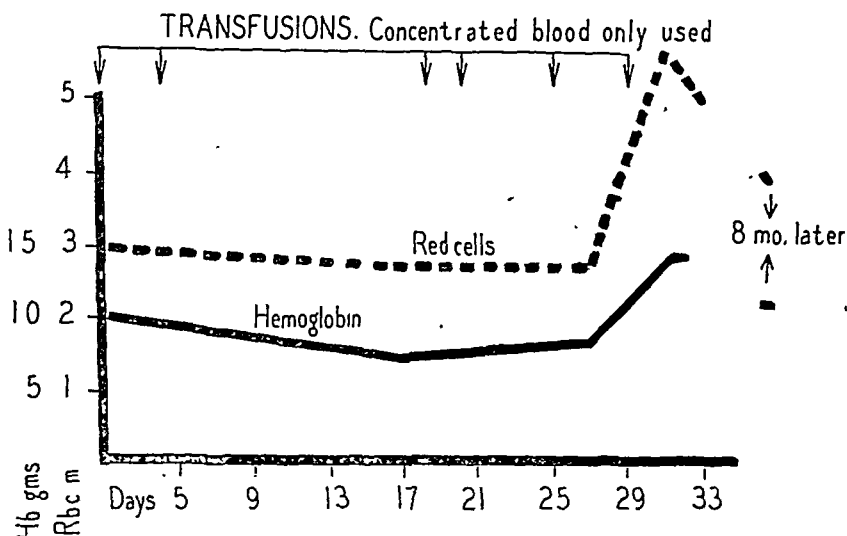


Fig. 3.

INDICATIONS

1. Hemolytic anemias
 - a. Lederer's acute
 - b. Erythroblastosis fetalis
 - c. Cooley's
 - d. Target cell
 - e. Familial hemolytic
 - f. Sickle cell icterus
 - g. Macrocytic
 - h. Acquired
 - (1) Poisoning
 - (2) Infection
2. Aplastic anemia
 - a. Infectious
 - b. Constitutional
3. Von Jaksch
4. Anemia of the premature
5. Severe nutritional
6. Hemophilia
7. Thrombopenic purpura
8. Hemorrhagic disease of the newborn
9. Hemorrhagic nephritis
10. Traumatic hemorrhage
 - a. Newborn infant
 - (1) Cord
 - (2) Circumcision
 - (3) Liver
 - b. Child
 - (1) Rupture of spleen
 - (2) Post tonsillectomy
11. Rheumatic fever

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AN EVALUATION OF THE DISTINCTION IN THE CLINICAL COURSE AND THE TREATMENT OF ERYTHROBLASTOSIS AND ICTERUS GRAVIS

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FOR many years two separate entities seen in newborn infants were described. Both were usually fatal. Both were associated with a hemolytic anemia. One was known as icterus gravis. The other was called erythroblastosis fetalis. Diamond and associates¹ in 1932, associated these two diseases in twins and in families so extensively that they concluded that these diseases, as well as hydrops and "anemia of the newborn," were varying stages of the same disease. In 1940 Levine and Katzin² demonstrated a relationship between the Rh factor and erythroblastosis fetalis. This bore out Darrow's³ theory of the possible cause of the syndrome. Since then, many controversies have arisen because of different conceptions or understandings of the disease.

Clinicians have made their own decisions in their studies, mostly on a basis of severity; as to which cases might be included in any study of the disease, often disregarding the studies of Diamond and associates,¹ which were by far the most accepted at the time that the Rh factor was introduced to medicine. Pathologists^{4, 5} have set up standard requisites for the diagnosis of erythroblastosis fetalis, standards which other pathologists^{5, 6} have used to limit Rh-negative incompatible as the etiology. The result has been varying, credit frequently being given to the Rh factor clinically as the sole etiology of the disease. Since the printed word backed by extensive material has been the accepted authority in medicine to date, we⁷ investigated a group of cases, all of which would well fall into the classification of Diamond and associates,¹ and found only 67 per cent of the cases could be demonstrated to have the Rh-negative setup. For this, our work has been questioned by a pathologist⁸ with a different set of rules for inclusion or exclusion of cases in this syndrome, in spite of the fact that pathologists⁶ constantly bring out pathological findings in newborn infants of erythroblastic excess in the liver and other conditions, which are in no way related to this disease.

It is, therefore, worthy of point today for the benefit of the physician who sees the living patient to give a description of the following two strikingly different syndromes seen in the newborn, which in the majority of cases bear up the Rh syndrome but whose courses, and particularly the treatment and outcome, vary distinctly; two clinical syndromes, which, if proved to be different diseases, would clear up a greatly muddled subject and would go far in truly evaluating the role of the Rh factor.

TYPE I

At birth or in the first day of life, an obvious jaundice develops in the newborn. Some edema is present occasionally and in this case, too, there is a

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conspicuous paleness to the baby. But far more commonly associated with the jaundice are petechiae of varying size. Because of these observations, blood counts are obtained. There is found a varying degree of anemia associated with a marked erythroblastosis. A history is presented of previous jaundiced babies in the family or of previous deaths of newborn babies in the family involving very seldom, however, the first born. If left untreated, the baby becomes more jaundiced, very toxic, more anemic, and death ensues in about three days. His nutrition is either normal or poor. When treated with blood transfusions within the twenty-four hours in sufficient amounts, there is very marked improvement in the blood picture. The number of erythroblasts drops and the red count drop slows up. Repeated transfusions continue to control and improve the blood picture but the jaundice markedly increases for three or four days; during this time the stool, which has been dark, becomes lighter in color. More petechiae occur, and the prothrombin time increases.

TYPE II

The second syndrome starts differently. This baby is born an exceptionally well-nourished baby. His color is good and during the first twenty-four hours, there are no alarming findings. However, in the second twenty-four hours, the baby rapidly becomes jaundiced; by the third day, the jaundice is extreme and there is very frequently, to a greater or lesser degree, retraction of the baby's neck. Examination reveals a normal blood count or a mild anemia with but a few erythroblasts. The baby develops from this point a gradual anemia which, if sufficiently neglected, will be associated with a definite erythroblastosis after it drops below three million. The spleen becomes enlarged and the prothrombin time remains high regardless of the administration of vitamin K. Throughout, nutrition is rarely a problem. The spinal fluid is high in bile pigment. The immediate outlook in these cases is good but, unfortunately, the final outlook is poor. The evidence of brain damage from the irritation of bile pigment results in a residual very much as that seen in the well-known spastic. Hemorrhage of any sort is rare in these babies, in spite of the high prothrombin time.

In Type I the meningismus has not been seen by us. The anemia develops more rapidly; enlargement of the spleen is often present at birth; and the hemorrhagic tendency is greater.

These distinctions are very important to the clinician treating the newborn infant.

In the first disease transfusions are needed immediately, preferably of concentrated blood cells, typed and matched.

In the second condition the value of blood given immediately is debatable. It may not be needed because of obvious lack of marked anemia. However, its elements may materially stop the obvious hemolytic process. It therefore should be given in smaller amounts than in the first type or it may contribute to the total excess of bile pigment in the circulation. What is extremely more important is to attempt to protect and stimulate an inefficient liver. Therefore, the use of glucose subcutaneously early and repeatedly, and the administration of choline

chloride⁹ from birth is of extreme importance to prevent the fatty degeneration.^{9, 10} No doubt, many other clinical findings should be listed, but those given suffice to demonstrate the clinical difference as seen by the pediatrician.

It is our belief because of the present emphasis on our transfusion therapy of "select" bloods that the clinical distinction given here deserves restitution regardless of the classification of Diamond and associates of the two conditions being one and the same, and regardless of whether the Rh-negative factor is the cause in 50, 75, or 90 per cent of the cases.

CASE REPORTS

Example of Type I

Baby S.—At birth, June, 1943, the baby weighed 7 pounds, 2 ounces. The cry was spontaneous; there were no anomalies; vernix was yellow tinged; there was edema of the scrotum.

Three hours after birth there were petechiae on the thighs and arms. Examination of the blood revealed a red blood count of 3,700,000; white blood count corrected, 10,000; erythroblasts, 350 per 100 white blood cells found in stained blood smear.

Eight hours after birth the baby was transfused with 75 c.c. of concentrated blood cells.

Sixteen hours later the red blood count was 3,400,000. The baby was markedly jaundiced. The blood transfusion was repeated.

Twenty-four hours later (baby 48 hours old) the red blood count was 3,400,000; hemoglobin, 70 per cent; icteric index, 90; erythroblast count, 100 per 100 white blood cells.

On the fourth day the red blood count was 3,300,000; hemoglobin, 70 per cent; erythroblasts, 50 per 100 white blood cells. The baby was still toxic, jaundiced with more greenish tinge, eating poorly. Concentrated blood cell transfusion, 100 c.c., was given.

On the fifth day the red blood count was 4,000,000; hemoglobin, 82 per cent; erythroblasts, 10 per 100 white blood cells.

On the sixth day the red blood count was 4,100,000; hemoglobin, 80 per cent.

On the eighth day the red blood count was 4,000,000; hemoglobin, 80 per cent; icteric index, 70. The baby was eating better.

On the thirteenth day, the red blood count was 3,800,000; hemoglobin, 80 per cent, icteric index, 50. The baby was gaining weight.

On the twentieth day, the red blood count was 3,300,000; hemoglobin, 65 per cent; icteric index, 30. The baby was gaining slowly. Blood, 70 c.c., was given by transfusion.

On the twenty-third day, the red blood count was 4,000,000; hemoglobin, 75 per cent.

Thereafter, the jaundice became undetectable. Iron administration was necessary about one month later because of a fall in hemoglobin. Otherwise, no further specific care was needed.

During the entire time, the baby received 10 grains of choline chloride daily and subcutaneous glucose daily for the first ten days of life.

Family History: There were two previous births with both children living and well. There was no history of jaundice. The mother showed strong Rh antibodies titer. The mother was Rh negative; the father, Rh positive; the baby, Rh positive.

Example of Type II

Baby J.—At birth, Oct. 10, 1944, the baby weighed 7 pounds, 10 ounces. The cry was spontaneous. There were no anomalies or other pathologic physical findings.

Twenty-four hours after birth, there was definite yellow discoloration of the skin.

Forty-eight hours after birth, the red blood count was 4,600,000; hemoglobin, 100 per cent; erythroblasts, 5 per 100 white blood cells; white blood count corrected, 12,000.

On the third day of life, the jaundice was extreme. The icteric index was not accurately estimable. The baby was drowsy but accepted food. Weight gain of one ounce occurred from the previous day. The diapers were deeply stained. The head was slightly retracted with

no bulging of the fontanel. The red blood count was 4,100,000; hemoglobin, 80 per cent; erythroblasts, 5 per 100 white blood cells. Subcutaneous glucose was given three times a day.

On the fourth day, the red blood count was 4,000,000; hemoglobin, 75 per cent.

On the fifth day, the red blood count was 3,700,000; hemoglobin, 65 per cent. The jaundice was extreme. The head was still retracted. Spinal puncture revealed no appreciable red blood cells but was heavily bile stained. The blood culture was negative; blood Wassermann was negative. Stools were yellow. Matched blood, 50 c.c., was given by transfusion.

On the sixth day, the red blood count was 3,900,000; hemoglobin, 70 per cent. The jaundice was detectably less. The neck was not quite as stiff. The stools were paler in color. The nutrition was good.

On the tenth day, the baby was still markedly jaundiced. The neck, however, was more relaxed; the stools were darker in color; and the red blood count was 3,400,000; the hemoglobin, 60 per cent.

On the twelfth day, the red blood count was 3,000,000; icteric index, 70. The spleen was palpable. The baby was more alert. Blood, 75 c.c., was administered.

During the entire time the baby received subcutaneous glucose daily and choline chloride, grains 10, daily. The jaundice remained in some degree until the baby was 1 month of age. At this time a third transfusion seemed advisable since the hemoglobin had fallen to 55 per cent and the red blood count to 2,900,000. Following this, recovery was uneventful, but the child's neuromuscular development was slower than average.

Family History: Two living and well children; two children dead, one of whom died immediately following birth, supposedly with edema.

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THE USE OF RH-POSITIVE BLOOD CELLS IN THE TREATMENT OF ERYTHROBLASTOSIS FETALIS

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WITH our present knowledge, erythroblastosis fetalis may be said to be a disease of two phases. First, acute hemolytic anemia, and second, liver dysfunction. Any acute hemolytic anemia needs red blood cells in large quantities quickly. With the development of the scalp vein technique for transfusing infants, the mortality rate of this disease began to drop. However, recognition of the mechanism back of the hemolysis has caused great concern over the selection of the *type* of blood for transfusion.

Soon after the original publication of Levine and Katzin¹ in regard to the Rh factor in this disease, we were fortunate in obtaining from a mother of a baby with erythroblastosis a very potent anti-Rh serum. With this serum and the cooperation of all of the hospitals in St. Louis, we had the opportunity of examining the blood and treating a proportionately large group of cases of hemolytic anemia of the newborn with severe icterus. We found during this study² that the identification of Rh type accordingly required particular technique which at that time fortunately was available to us at St. Louis University. At that particular time, Dr. Gallagher examined the blood of the freshman and sophomore medical school classes and obtained five Rh-negative donors. The blood of these men was administered in a number of cases of erythroblastosis. Clinically, the results were not any more impressive than when we used Rh-positive blood. However, recent articles by Weiner³ have given great import to the use of Rh-negative blood as a treatment of the infant with erythroblastosis fetalis. On the other hand, to evaluate comparatively the use of Rh-positive blood (which is always more readily available) is still the interest of the authors.

The following factors influenced our thinking:

1. Rh-negative blood for transfusion is not universally readily available.
2. We have never felt that Rh studies on blood, up to the present time at least, were too reliable when done rapidly in the hospital, and since the bacteriology department of the University cannot do them on demand, we have not had them available when most needed.
3. We were impressed repeatedly with the results obtained with father's blood. One case was previously reported in an article on the treatment of the disease with choline chloride in the *Southern Medical Journal*.⁴ In many cases in which the obstetrician had given one transfusion of father's blood before the patient was seen by us, the result was quite remarkable.

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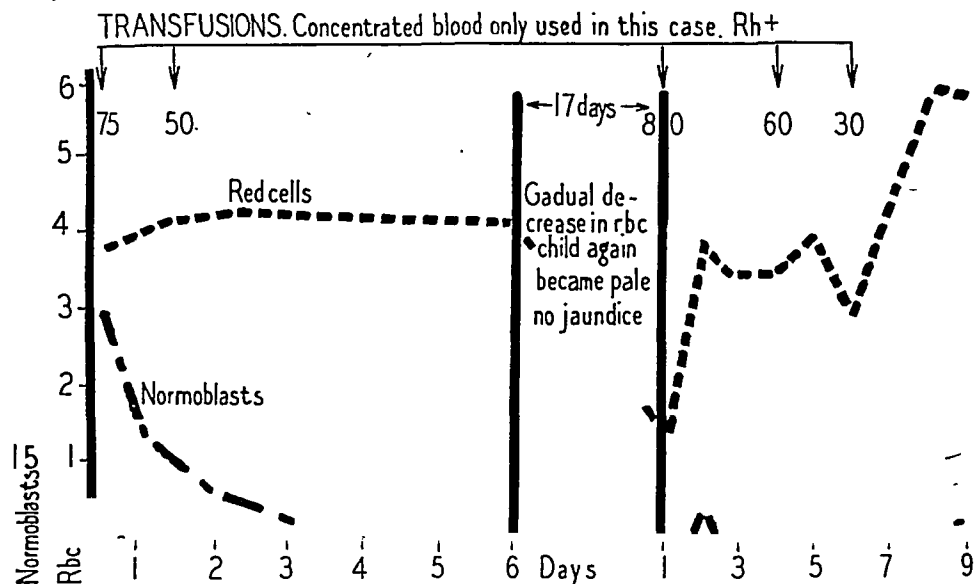


Fig. 1.—Case 1. Pale at birth. Jaundice appeared in twenty-four hours, persisted for ten days. Mother's blood, Rh negative; baby's blood, Rh positive. Follow-up reveals no anemia. No transfusion reactions.

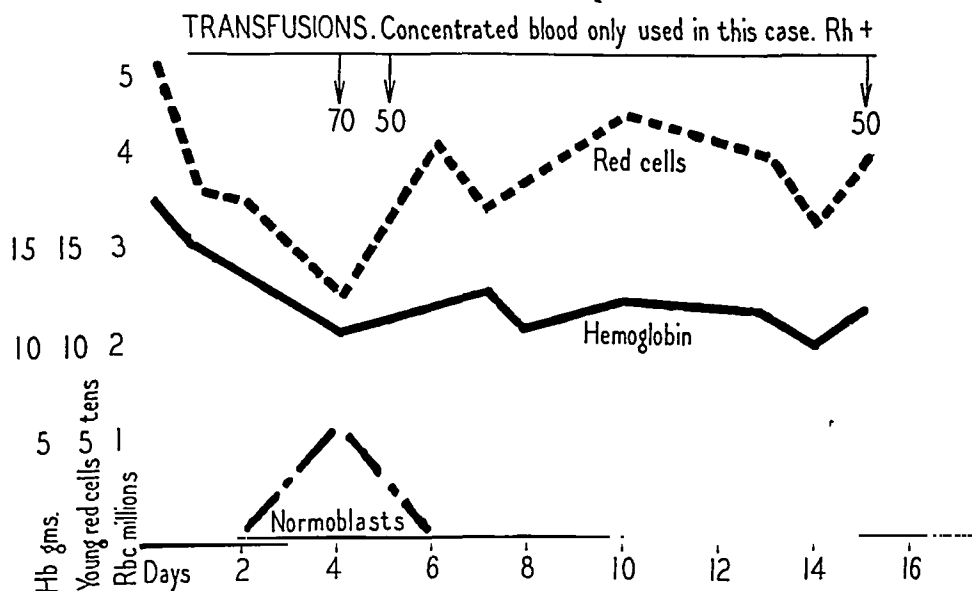


Fig. 2.—Case 3. Not jaundiced or pale at birth. Jaundice appeared in twenty-four hours and persisted for ten days. Pale twenty-four hours after birth. Mother's blood, Rh negative; baby's blood, Rh positive. Follow-up reveals no anemia. No transfusion reactions.

4. If one accepts Diamond, Blackfan, and Baty's² broad classification of this syndrome, one finds many cases in which the baby's mother is not Rh-negative. This we have observed and reported.²

5. We have not been impressed with the results of our original administration of Rh-negative cells. The erythroblast count was slow in dropping.

6. Our thought has been as follows: The baby's blood in the vast majority of incidences of erythroblastosis is Rh positive. This blood is therefore susceptible to the Rh antibody. This Rh antibody is limited in amount in the baby for it has been passively received from the mother, from whom all connection has been severed at the time of birth. (Breast feeding is contraindicated.⁶)

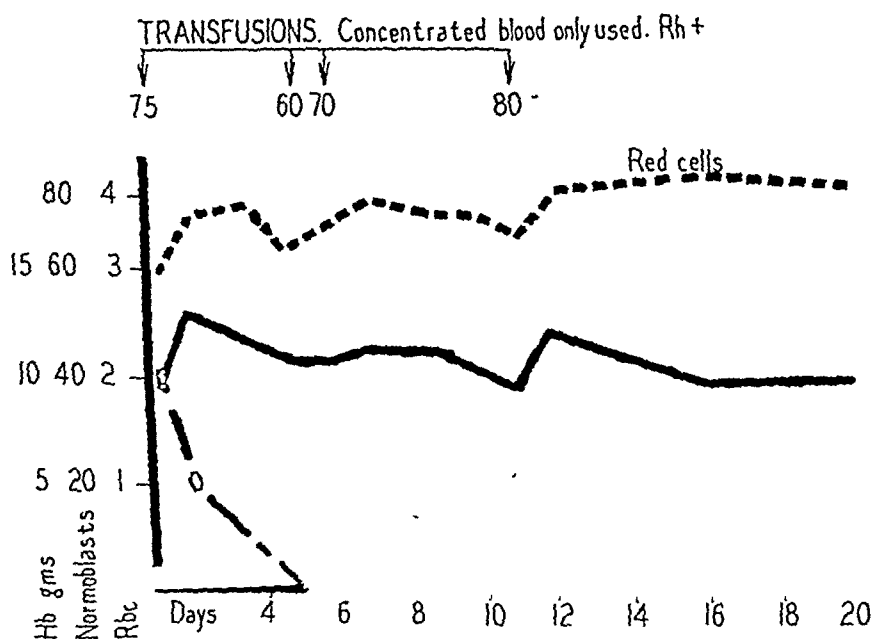


Fig. 2.—Case 4. Jaundiced twenty-four hours after birth; jaundice persisted for eight days. Mother's blood, Rh negative, baby's blood, Rh positive. Two weeks later red blood count, 2.80. Concentrated blood, 110 c.c. Count, 4.20. No subsequent anemia. No transfusion reactions.

This antibody eventually is completely absorbed by the baby's red blood cells. This produces an extreme strain on the baby's blood-forming organs, one which may be reflected by hemopoietic exhaustion for an indefinite time. This is the only thing that can happen when Rh-negative blood is used as a means of treatment since its very meaning implies its noninterference with the activity of the Rh antibody. If Rh-positive cells are used, some of the Rh antibody is absorbed by this artificially donated antigen. The massive damage to the baby's own cells is reduced, the reduction depending on the amount and the rapidity of administration of the Rh-positive cells. True, there would be destruction, as a result of the administration of all these Rh-positive cells. The total destruction of cells could not be greater in the one instance over the other. Therefore, the damaging effect on the liver of massive blood destruction could not be greater when artificially supplied Rh-positive cells are used than when only the baby's

Rh-positive cells are destroyed, and the massive damage to the baby's own cells could not help but be reduced. If the antibody is specific for the baby's cells, then the Rh-positive blood we administer like Rh-negative blood cells will be equally usable by the baby. We do not know the whole mechanism of Rh-positiveness of red blood cells, and consequently it seems rational to give the baby

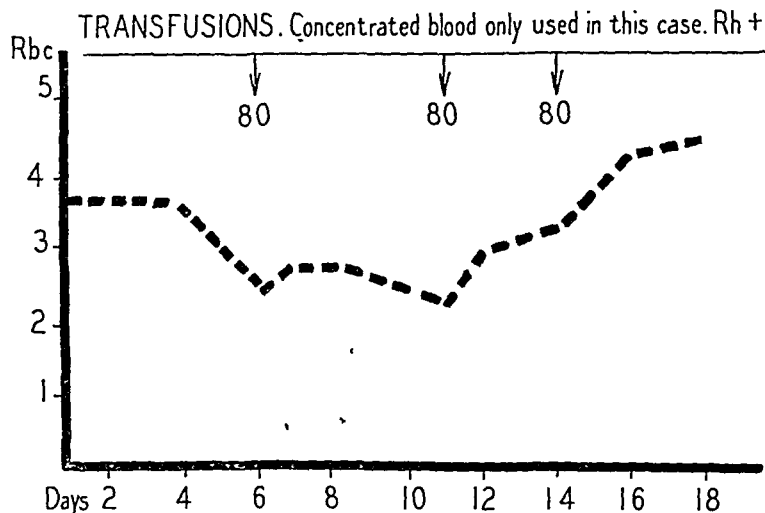


Fig. 4.—Case 5. Jaundiced twenty-four hours after birth. Jaundice persisted for eleven days. Mother's blood, Rh negative. Baby's blood, Rh positive. Follow-up reveals no anemia. No transfusion reactions.

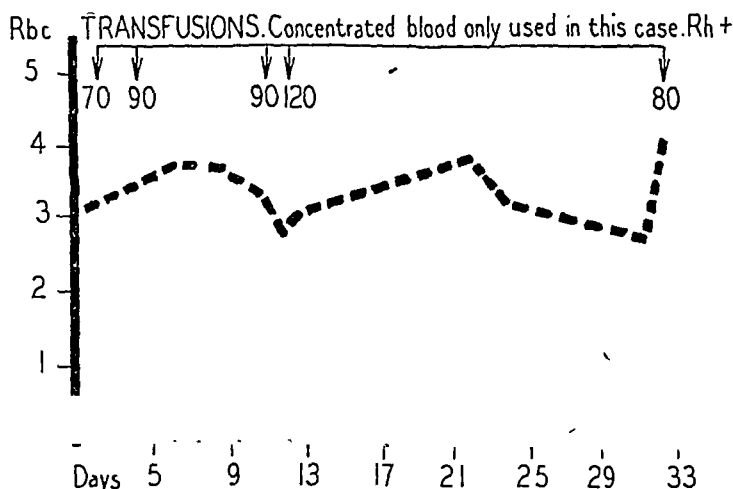


Fig. 5.—Case 6. Jaundiced shortly after birth for ten days. Mother's blood, Rh negative; baby's blood, Rh positive. Follow-up reveals no anemia. No transfusion reactions.

blood which is identical with his own, since 85 per cent of all persons' blood is Rh positive. Since the incidence of this disease is being more frequently recognized, we feel it important to call attention to these facts, since the literature today would imply that the use of Rh-positive blood for these babies is contra-indicated.

Again, since we are dealing with an acute hemolytic anemia, the concentration of red blood cells in the transfusing fluid is of great importance.

The accompanying graphs (Figs. 1 to 5) demonstrate the response of a typical case to Rh-positive concentrated cell transfusion. When a blood count of over 4,000,000 and a hemoglobin of 85 per cent were maintained, no further transfusions were administered. If, however, a drop was observed or the number of erythroblasts increased, blood was again administered.

We conclude:

That Rh-positive blood can very satisfactorily be used to treat erythroblastosis fetalis.

That concentration of the red blood cells reduces the frequency and the volume of transfusions necessary.

That concentration can be simply obtained by syphoning off the plasma down to a centimeter of the cell level in refrigerated blood.

That such cell concentrations do not require any different method of administration or preparation for use.

That such transfusions do not produce any clinical evidence to contraindicate their use.

All babies with this disease, in our opinion, have either primary or secondary liver dysfunction.⁴ Glucose is therefore an indicated adjunct to treatment. Choline chloride, which supplies, according to our knowledge today, the CH_3 radical for fat mobilization, is particularly valuable in preventing the fatty degeneration consistently found in post-mortem examinations in this disease. It is our opinion that it should be used constantly throughout the course of the disease.

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APPRAISAL OF TREATMENT OF *HEMOPHILUS INFLUENZAE* TYPE B MENINGITIS WITH SPECIFIC RABBIT SERUM AND SULFONAMIDES

BASED ON OBSERVATION OF SIXTY CASES

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IN SPITE of the fact that since the advent of type-specific rabbit serum and sulfonamides, the prognosis in meningitis due to *Hemophilus influenzae* has radically changed, many pertinent problems still remain to be solved. For instance, the case fatality rate in infants continues to be relatively high; the value of intrathecally injected serum is still a moot question; little is known with respect to measures that prevent complications and sequelae; it is as yet difficult, if not impossible, to determine in advance the minimal and optimal amounts of antiserum and sulfonamides required to eliminate the organisms; and, finally, tests are not available which permit an appraisal of the virulence of the infecting bacillus. So many factors influence the outcome of the disease that it becomes rather difficult to evaluate the results obtained with certain therapeutic methods. This is well brought out by the fact that the reported case fatality rates in patients treated with type-specific serum and sulfonamides vary from less than 20 per cent up to 50 per cent (Table I).

A relatively large number of patients suffering from this disease were treated at this hospital with Alexander's type-specific serum and various sulfonamide compounds. In order to obtain additional information on the value and particularly the shortcomings of this form of specific therapy, the beneficial and adverse effects resulting from intrathecally injected antiserum, and the incidence of complications and sequelae, these cases were utilized for analysis. The data obtained are incorporated in this report.

This series is comprised of sixty consecutive cases of bacteriologically proved meningitis due to *H. influenzae* type B, treated with serum and sulfonamides. It is divided into two groups for the reason that the case fatality rate in patients treated until Sept. 30, 1944, was considerably higher than that of patients observed until May 31, 1945. The possibility presented itself that a comparison of the two groups might yield information leading to a better management of this malady.

As an index of the type of case and severity of the infection at the time therapeutic measures were instituted, it will be helpful to discuss briefly the age distribution of the patients, the incidence of bacteriemia and the spinal fluid glucose levels prior to therapy.

Tables II and III show the age distribution of the patients of both groups and the incidence of bacteriemia in fifty cases. It is worthy of note that *H.*

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TABLE I. CASE FATALITY RATES OF PATIENTS WITH H. INFLUENZAE MENINGITIS TREATED WITH TYPE-SPECIFIC RABBIT SERUM AND SULFONAMIDES

AUTHORS	NUMBER OF CASES	NUMBER OF DEATHS	CASE FATALITY RATE (%)
Alexander ¹	87	19	22.0
Turner ²	20	10	50.0
Comly and McKee ³	6	1	16.8
Birdsong, Waddell, and Whitehead ⁴	8	1	12.5
Boisvert, Fousek, and Grossman ⁵	26	4	15.4
Scully and Menten ⁶	9	4	44.0
Neter ⁷	7	3	42.9
Edmonds and Neter	60	20	33.0
Silverthorne ⁸	16	8	50.0
Smith et al.	28	2	7.0
Total	267	72	29.36

TABLE II. NUMBER OF FATALITIES AND RECOVERIES IN SIXTY CASES OF H. INFLUENZAE MENINGITIS

	AGES						TOTAL
	0-3 MONTHS	3-6 MONTHS	6-12 MONTHS	1-2 YEARS	2-5 YEARS	5 YEARS AND OVER	
Group I							
Recoveries	0	0	3	8	13	3	27
Fatalities	1	2	8	3	2	1	17
Group II							
Recoveries	0	1	3	4	4	1	13
Fatalities	1	1	0	0	1	0	3
Total							
Recoveries	0	1	6	12	17	4	40
Fatalities	2	3	8	3	3	1	20

TABLE III. BLOOD CULTURE IN H. INFLUENZAE MENINGITIS

	NUMBER OF PATIENTS WITH POSITIVE BLOOD CULTURES	NUMBER OF PATIENTS WITH NEGATIVE BLOOD CULTURES
Group I		
0-12 months of age	10	1
1 year and over	16	7
Group II		
0-12 months of age	5	1
1 year and over	8	2
Total		
0-12 months of age	15	2
1 year and over	24	9

TABLE IV. SPINAL FLUID GLUCOSE IN H. INFLUENZAE MENINGITIS

	GLUCOSE VALUES UP TO 20 MG. %	GLUCOSE VALUES OF 20 MG. % AND OVER
Group I		
Recoveries	13	5
Fatalities	12	4
Group II		
Recoveries	7	6
Fatalities	2	1
Total		
Recoveries	20	11
Fatalities	14	5

influenzae was found in the blood in 78 per cent of the patients and that bacteremia was somewhat more frequently present in infants than in older children. It is also evident that no striking differences exist between the two groups. The spinal fluid glucose levels prior to commencement of specific therapy were determined in fifty instances. The results are summarized in Table IV. It may be seen that values of less than 20 mg. per cent were encountered in relatively more patients of Group I than of Group II.

All patients received anti-*H. influenzae* type B rabbit serum (Squibb) intravenously, as well as one or more of various sulfonamide compounds. Twenty patients were given, in addition, antiserum intrathecally. The attempt was made throughout to administer intravenously adequate amounts of serum to maintain freely circulating antibodies in the blood and to procure sterilization of the cerebrospinal fluid.

Of the sixty cases treated, forty recovered from the infection and twenty succumbed. The case fatality rate, therefore, was 33½ per cent (Table I). If patients who died within less than twenty-four hours after commencement of specific therapy are excluded, the corrected case fatality rate is 28½ per cent. Among the twenty fatalities is one patient who probably recovered from the meningitis but died from a late complication, pneumonia, after hospitalization for two and one-half months. Post-mortem examination was not performed. As may be seen from Table I, the case fatality rates in Groups I and II were 38.7 per cent, and 18.7 per cent, respectively. Thus it appears that the treatment was more nearly successful in patients of Group II than of Group I. The question arises, however, whether this striking difference in the case fatality rates is due to variations in the management of specific therapy or to differences in the disease itself. Aside from the fact that spinal fluid glucose levels below 20 mg. per cent were found somewhat more often in patients of Group I than of Group II, no evidence of differences in the severity of the infection per se between the groups has been brought to light. It is quite possible that more intensive follow-up studies and therapy may be the reason for the lower case fatality rate in Group II.

From a clinical point of view, it is equally as important to consider the end results as it is the fatality rate. Aside from a complete check-up at the time of discharge from the hospital, a follow-up inquiry was made at the time of writing on all patients with residual lesions. Among the twenty-seven patients of Group I who recovered from the infection, twenty-three can be considered physically and mentally normal. Nine of the thirteen surviving patients of Group II made a complete recovery. Therefore, as far as complete recovery is concerned, the results accomplished in Group I were even slightly better than in Group II. The conclusion seems to be inevitable that the lower fatality rate in Group II is due to the survival of patients with complications and sequelae.

Of the three patients of Group I with residual lesions, one was completely deaf at the time of discharge and showed no improvement three years later. Partial deafness existed in the second case; no improvement was noted three

years later. The third patient had a minimal amount of facial paralysis at the time of discharge; one year later complete recovery had taken place.

In Group II there were four patients who recovered from the infection but showed sequelae at the time of discharge. One of these patients had a marked foot-drop; six months later this condition had decidedly improved. The other three cases presented the picture of hydrocephalus associated with definite mental retardation.

That combined serum and sulfonamide therapy did not always result in sterilization of the spinal fluid within a few days, is evidenced by the observation that in eleven of sixty patients, the culture remained positive for more than five days after treatment was commenced. The survival of *H. influenzae*, however, does not imply by necessity an unfavorable prognosis; five of the eleven patients recovered, including one whose spinal fluid cultures remained positive for eleven days. In this connection, it is important to call attention to the fact that the spinal fluid of five patients became only temporarily sterile and that microorganisms reappeared at various periods after specific treatment was discontinued. It is imperative, therefore, to follow such cases with repeated spinal fluid examinations and, when indicated, to continue or resume specific therapy.

An attempt was made to appraise the specific therapeutic measures individually; namely, intravenous and intrathecal serum therapy, as well as treatment with sulfonamides. The interpretation of the data, however, is complicated by the fact that the series is not comprised of groups of patients who were treated with one therapeutic method exclusively. First considered is the problem whether or not a relationship exists between the total amount of serum administered intravenously and the case fatality rate. The data obtained are summarized in Table V, which reveals that five of eleven patients recovered with 100 mg. or less, and eight of twenty-six patients succumbed in spite of the administration of 200 mg. or more of antibody nitrogen. It is evident, therefore, that other factors, apart from the total amount of serum administered intravenously, determine the outcome of the disease.

TABLE V. RELATIONSHIP BETWEEN AMOUNT OF TYPE-SPECIFIC SERUM* ADMINISTERED INTRAVENOUSLY AND OUTCOME OF DISEASE

	UP TO 100	101 TO 200	201 TO 300	301 AND OVER
Group I				
Recoveries	4 } 10	9 } 12	11 } 16	3 } 6
Fatalities	6 }	3 }	5 }	3 }
Group II				
Recoveries	1 } 1	8 } 11	3 } 3	1 } 1
Fatalities	0 }	3 }	0 }	0 }
Total				
Recoveries	5 } 11	17 } 23	14 } 19	4 } 7
Fatalities	6 }	6 }	5 }	3 }

*Amount in milligrams of antibody nitrogen.

Although in the majority of recovered cases, sterilization of the cerebrospinal fluid was preceded by the presence of freely circulating antibodies in the blood, the presence of these antibodies in the blood did not always indicate

absence of viable microorganisms. This confirms observations reported previously (Neter⁷).

For the evaluation of intrathecal serum therapy (single dose of 25 mg. of antibody nitrogen) twenty patients were available. Naturally, it is not possible to compare these patients with those who received the serum only intravenously, since the former group includes patients who did not respond to intravenous serum therapy alone. The series of the intrathecally injected cases, however, throws some light on the beneficial and adverse effects resulting from this therapy.

In four cases serum was given intraspinally or intracisternally at a time when many microorganisms were still present in the cerebrospinal fluid. These patients succumbed to the infection. It is interesting to note that in three instances, the spinal fluid cultures remained positive for *H. influenzae* during the entire period of observation. That the infection per se was not controlled by this form of therapy is evidenced by the results of the post-mortem examination of three patients, which revealed the presence of diffuse exudative meningitis. It is evident, therefore, that serum administered intrathecally to patients whose spinal fluid contained a considerable amount of specific soluble substance and numerous bacilli, was ineffective and may have been even detrimental. An adverse effect of intrathecally injected serum could have resulted from the action of the antibodies with the antigen present in soluble form as well as in the capsules of the bacilli, causing the formation of precipitates and clumps within the central nervous system. In 1938, Finland, Brown, and Rauh⁹ expressed the opinion that the administration of type-specific serum into the spinal canal in an otherwise untreated case of pneumococcal meningitis may result in harmful effects. Wheeler¹⁰ suggested that similar conditions may prevail in meningitis due to *H. influenzae*.

Of sixteen patients, who were given type-specific serum at a time when but few microorganisms were present in the spinal fluid, thirteen recovered and three succumbed to the infection. The role played by the intrathecally injected serum is difficult to appraise because preceding treatment had produced a decrease in the number of viable organisms. However, from certain clinical and bacteriologic observations of these cases, the impression is gained that serum injected intrathecally at the proper time resulted in a favorable response in certain instances. For example, in two cases the temperature had been ranging between 101 and 104° F. Within twenty-four hours after the administration of 25 mg. of serum into the cisterna, the temperature dropped to normal and remained so until the time of discharge. In other cases the intrathecal injection was followed by a gradual improvement. No clinical response was noted in three patients.

From a bacteriologic point of view it is interesting to note that sterilization of the cerebrospinal fluid followed the intrathecal injection of type-specific serum in three cases. The recovery of these patients may be due, indeed, to the action of the locally applied antibodies. Regarding those patients who responded favorably from a clinical point of view and whose spinal fluid cultures were found to be sterile prior to this form of therapy, two explanations

for the clinical improvement present themselves. It is conceivable that viable microorganisms were present in the meninges, although none could be demonstrated by culture, and that the serum caused elimination of these bacilli. On the other hand, the favorable clinical course may be due to nonspecific effects of the serum.

The question whether intracisternal administration of serum is preferable to intraspinal injections may be answered on the basis of the following observations. Of a group of six patients who received the serum intraspinally, five recovered, and among ten patients who were treated intracisternally, nine made a recovery. Thus no appreciable difference was noted between the two methods of intrathecal serum administration.

It is generally agreed that in meningitis due to *H. influenzae*, sulfonamides should be employed as adjuncts to serum therapy. The sixty patients of this series received one or several of various sulfonamide compounds, namely, sulfanilamide, sulfapyridine, sulfathiazole, and sulfadiazine. Forty-eight cases lend themselves to analysis. Ten patients were treated with sulfathiazole. The resulting levels in the blood ranged from 5 to 8 mg. per cent. Of these patients, six recovered and four succumbed to the infection. Of the thirty-eight patients treated with sulfadiazine, twenty-nine recovered and nine died. The blood levels ranged between 10 and 25 mg. per cent. Although the difference in the case fatality rates is very slight, if at all statistically significant, it appears that sulfadiazine is preferable to sulfathiazole.

Regarding reactions to the anti-*H. influenzae* serum and the sulfonamides, the following observations have been made. In no instance was sensitivity to the serum so marked as to render its administration impossible. Immediate reactions to the serum, consisting of cyanosis, labored respiration, wheezing, cough, and urticaria, were encountered in seven instances. The reactions generally were mild and promptly relieved by adrenalin. Delayed serum reaction (urticaria-like rash) was encountered in eight instances. The intrathecal administration of serum caused reactions in three cases; namely, a generalized convulsive state in two and a sudden rise in temperature in the third patient. Fatal reactions were not encountered.

Complications other than cyanosis resulting from chemotherapy were observed in fourteen of the sixty patients. Hematuria occurred in thirteen instances; it was promptly controlled by reducing the amount of the drug, increasing the fluid intake, and alkalinizing the urine.

In only one instance was the influenza bacillus infection associated with a purulent lesion outside the central nervous system. This occurred in a 15-month-old white female who was comatose and in a moribund condition on admission. Multiple petechiae were noted. The patient was in shock, the blood pressure being 70/30 mm. Hg. Following the administration of type-specific serum, sulfadiazine, plasma, whole blood, and adrenal cortical extract, the patient gradually improved and recovered from the meningitis. However, on the fifteenth day of hospitalization the blood culture again became positive and the child developed purulent arthritis of the right knee joint. *H. influenzae* was recovered from the exudate. Following the intravenous adminis-

tration of 250 mg. of antibody nitrogen the patient recovered from this complication. At the time of discharge, hydrocephalus was present and the child was mentally retarded, as a sequela of the meningitis.

Two additional cases are included here because they illustrate that the classical picture of the so-called Waterhouse-Friderichsen syndrome or its initial stage, may be due to an infection with *H. influenzae*. These two patients are not included in the series itself, since they succumbed to the infection before it was possible to commence specific serum therapy. In one of these cases, post-mortem examination revealed the presence of massive diffuse hemorrhages of both adrenal glands. Meningitis, bacteriologically proved to be due to influenza bacillus type B, was also present. Interestingly enough, there were no petechiae. In the second case, post-mortem examination showed a superficial hemorrhage into the right adrenal gland; the left was normal. Had the child lived longer, more extensive hemorrhages might have developed.

DISCUSSION

The present series of sixty bacteriologically proved cases of meningitis due to *H. influenzae*, treated with type B specific antiserum and sulfonamides, illustrates the advances made in the treatment of this malady, as well as certain important failures. The effectiveness of these therapeutic agents has been definitely established and is reflected in this series by an uncorrected case fatality rate of 33½ per cent as compared with over 90 per cent in untreated cases. It is worthy of note that 19 of 35 patients under 2 years of age recovered. This recovery rate of approximately 54 per cent compares favorably with the recovery rate of 3 per cent of 152 cases not treated by specific measures. On the other hand, it is evident that in spite of all attempts to initiate specific treatment as soon as possible, to procure an adequate antibody titer in the patient's blood, and to maintain fairly high sulfonamide levels, one-third of these patients succumbed to the infection. Failure of therapy is particularly striking in young infants: only one of six patients less than 6 months old recovered from this illness. This age group presents the greatest challenge to therapy.

Another aspect of considerable importance in the cases presented here is the relatively high incidence of complications and sequelae. Seven of these sixty patients belong to this group. Aside from facial paralysis, partial or complete deafness, and foot drop, the most serious complication of the disease was marked hydrocephalus associated with mental retardation. It is not possible to state with any degree of certainty whether the development of hydrocephalus could have been prevented by a different management of therapy. It must be stressed that two of the three patients were given antiserum intrathecally at a time when but few microorganisms were present in the spinal fluid with a correspondingly low content of specific soluble substance. Whether or not this treatment contributed to the development of hydrocephalus, is a moot question that deserves further attention. It is felt that even with the experiences just mentioned, this form of treatment for well-selected cases should not be condemned at the present time. Clinically, several

patients responded favorably to the intrathecal administration of serum, and in several instances this form of therapy was followed by sterilization of the spinal fluid. The observations here reported seem to substantiate the opinion expressed by Finland, Brown, and Rauh,⁹ as well as by Wheeler,¹⁰ to the effect that serum injected intrathecally at a time when many organisms are present in the spinal fluid may have deleterious effects. Four such patients were observed all of whom succumbed to the infection. Of course, it is possible that the prognosis in these cases was poor, precisely because so many organisms were present. However, other patients whose spinal fluid contained equally as many microorganisms made an uneventful recovery.

From the reports in the literature and the experience with these sixty cases, the following conclusions may be drawn: (1) It is imperative that a diagnosis be made at the earliest possible time. (2) Treatment should consist of the administration (either intravenously or intramuscularly) of type-specific rabbit serum and sulfonamides, preferably sulfadiazine. (3) Adequacy of therapy should be established not only by the examination of the blood for free antibodies, but also by complete studies of the cerebrospinal fluid. Recrudescences should be recognized as soon as possible and dealt with accordingly. (4) Bacteriologic and clinical observations indicate that in certain selected patients intrathecal serum administration may be used with benefit to supplement intravenous serum therapy. Possible deleterious effects must be kept in mind and further investigations into this problem are definitely needed. Intrathecal injection of serum to patients whose spinal fluid contained many bacilli proved to be entirely ineffective and probably harmful. (5) Studies on the prevention of hydrocephalus as a complication or sequela of this malady are urgently needed. (6) The effectiveness of penicillin and other antibiotic therapy in this malady requires further investigation.¹

SUMMARY

Sixty cases of *H. influenzae* type B meningitis in infants and children treated with Alexander's type-specific rabbit serum and sulfonamides were analyzed. These cases were divided into two groups: Group I is comprised of all cases up to Oct. 1, 1944, and Group II from Oct. 1, 1944 to May 31, 1945. The following data were obtained:

1. Bacteriemia was present in thirty-nine of fifty cases (78 per cent).
2. The case fatality rate was $33\frac{1}{2}$ per cent for the entire series, 38.7 per cent for Group I, and 18.7 per cent for Group II; for children under 2 years of age it amounted to 45.7 per cent.
3. Of the sixty patients, thirty-two had completely recovered at the time of discharge from the hospital. There was no appreciable difference in the rate of complete recoveries between the two groups.
4. The following complications and sequelae were encountered: purulent arthritis, facial paralysis, partial and complete deafness, foot drop, and hydrocephalus associated with mental retardation.
5. The total amount of intravenously injected serum was not the sole factor responsible for the outcome of the disease. Of particular significance is

the fact that eight of twenty-six patients succumbed in spite of the administration of more than 200 mg. of antibody nitrogen, including three of seven patients who received more than 300 mg.

6. All four patients who received serum intrathecally, at a time when many microorganisms and a correspondingly large amount of specific soluble substance were present in the spinal fluid, succumbed to the infection. The possible deleterious effects of this therapy have been discussed. Intrathecal injection of serum in patients whose spinal fluid contained but a small number of microorganisms or none at all was followed, in several instances, by clinical improvement and sterilization of the spinal fluid. The possibility that this form of therapy may have been responsible, in part at least, for the development of hydrocephalus in two patients has been considered.

7. Immediate reactions to the type-specific serum injected intravenously were encountered in seven instances; delayed reactions, in eight. Intrathecal injection of serum resulted in convulsions in two patients and fever in one.

8. Two cases, presenting, respectively, the initial stage and the classical picture of the Waterhouse-Friderichsen syndrome as seen on post-mortem examination, have been reported.

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AURICULAR FIBRILLATION IN INFANCY

REPORT OF A CASE WITH FLEETING PAROXYSMS

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IN 1938 Goldbloom and Segall¹ reported a case of auricular fibrillation in an infant 3 months old and stated that an exhaustive search of the literature had not revealed a report of a single case of auricular fibrillation in the first year of life. We wish to report a second case first observed by us in 1943; to the best of our knowledge no other report has appeared in the literature since 1938. This case is of interest not only because of the rarity of auricular fibrillation in infants, but also because the irregularity was due to fleeting paroxysms of auricular fibrillation of the type described by several workers and discussed thoroughly by Wolferth in 1925.²

CASE REPORT

K. C., born April 12, 1943, was first seen by one of us when she was 2 months of age. The birth history revealed that she had been a blue baby. Except for a marked irregularity of the heart, physical examination was not significant. The heart action was very rapid and the arrhythmia of the totally irregular variety. No murmurs or cardiac enlargement could be made out at this time and there was no cyanosis present.

On July 9, 1943, when the baby was 3 months old, an electrocardiogram (Fig. 1) was made. This tracing showed paroxysms of auricular fibrillation with a rapid ventricular rate; the paroxysms were very short and followed a conducted beat. At this time, digitalization was begun, starting with a daily dose of $\frac{1}{2}$ grain. Small dose therapy was continued for several months during which time no apparent effect on the arrhythmia or on the rapid ventricular rate could be detected. The rate, counted with some difficulty, varied between 140 and 200. When the child was 5 months old, for the first time a high-pitched, systolic murmur was heard in the second interspace to the left of the midline. A month later on Oct. 12, 1943, a second electrocardiogram showed little change over the first. There was still marked irregularity due to transient auricular fibrillation. At this time the murmur had increased in intensity and could be heard over the whole precordium. There was an associated systolic thrill present. An x-ray examination of the chest revealed the cardiac shadow to be of the "Dutch shoe" type and showed some enlargement.

Since the rapid cardiac rate showed little tendency to slowing and the baby's general condition seemed to be worse, it was decided to use larger doses of digitalis. For a period of several weeks a daily dose of $1\frac{1}{2}$ grains was used and this appeared to keep the rate below 140 and the rhythm slightly more regular. Improvement continued until the middle of November when vomiting started, and in spite of discontinuing digitalis, persisted to such an extent that hospitalization was found necessary. On Nov. 20, 1943, the baby was admitted to the Jewish Hospital of Philadelphia on the pediatric service of Dr. Robert Schless. A few days after admission, quite suddenly, the baby died. Unfortunately a post-mortem examination could not be obtained.

DISCUSSION

Although a review of the literature indicates that auricular fibrillation is extremely rare in the newborn, irregularities, including auricular fibrillation have been described during fetal life. Hyman³ secured phonocardiograms of three types of arrhythmias in the fetus—sinus arrhythmia, ventricular extrasystoles, and auricular fibrillation. Extrasystoles^{4, 5, 6, 7} and auricular flutter^{8, 9}

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have been reported in infants, and instances of paroxysmal tachycardia¹⁰ sometimes with extremely rapid ventricular rate have also been described.

In the case reported by Goldbloom and Segall,¹ auricular fibrillation was demonstrated at the age of 3 months in an infant whose heart was otherwise normal. Digitalis effectively reduced the ventricular rate and normal rhythm was restored spontaneously in the twelfth month and persisted to the date of publication. Our case differs in that the arrhythmia occurred in an infant with congenital heart disease and also because the paroxysms of fibrillation were

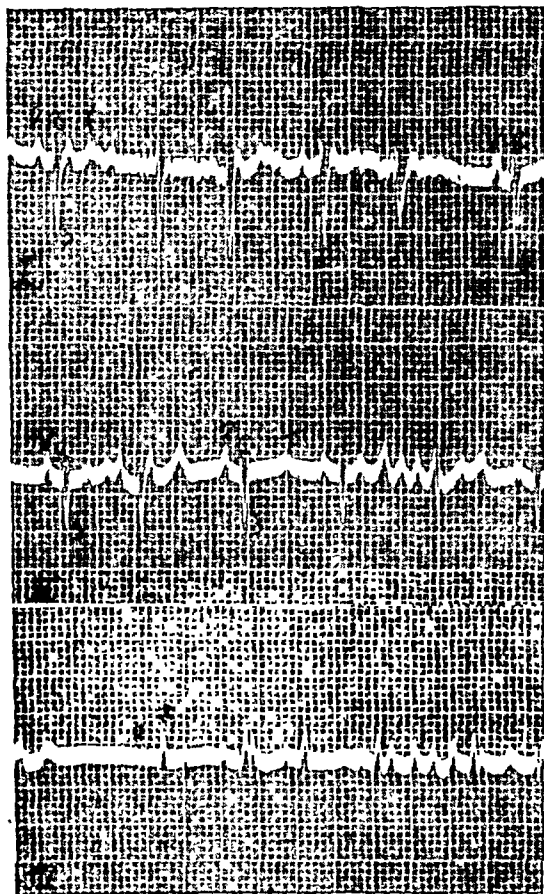


Fig. 1.

Although digitalis was effective in Goldbloom and Segall's case, no marked reduction in ventricular rate was noted in our case. In man auricular fibrillation and flutter are usually precipitated by auricular extrasystoles. Although circus rhythm occurs in auricular muscle which is in the stage of what Garrey¹¹ called the "fibrillary state" and such a state is most likely to exist at the time of extrasystoles, Garrey stated that auricular fibrillation may also be precipitated by a normal impulse from the sinus node. Garrey showed that "such fibrillary beats are initiated in the normal way from the normal pacemaker, that

the impulse shuttles back and forth through the auricular muscle producing rapid oscillations, which may stop before the next impulse arises so that the normal rhythm is not disturbed in the least." The paroxysms in our case appeared to be initiated by a normal impulse rather than extrasystoles. In 1918, Semerau¹² reported two cases of short paroxysms of auricular fibrillation which were thought to be precipitated by normal sinus impulses and, in 1940, Hecht and Johnston¹³ reported a case of fleeting paroxysm of auricular flutter initiated by a normal sinus beat.

If auricular fibrillation occurs only when the auricular muscle is in the so-called "fibrillary state" one may speculate that the short paroxysm may be due to a temporary return to the normal state or to a derangement of the mechanism necessary to maintain fibrillation. Although very few cases of fleeting paroxysms of auricular fibrillation or flutter have been reported in the literature, this may be due to the difficulty of recognizing such brief paroxysms or they may be too brief to record. In 1925, Wolferth found only four cases reported in the literature with electrocardiograms that left no doubt as to the correctness of the interpretation and reported another case; in the same year Wolferth¹⁴ reported two cases with fleeting paroxysms of auricular flutter.

Permanent fibrillation is rarely observed in normal hearts, but it is not unusual to observe paroxysmal fibrillation in adults whose hearts are otherwise normal. However, neither type had been reported in infants until 1938 when Goldbloom and Segall reported their case, attesting to the rarity of this condition in infancy and the possibility that when fibrillation does occur in infants it is usually too fleeting to be recognized or recorded. Garrey stated that the tendency to recover from fibrillation is in inverse ratio to the tissue mass, probably because greater mass and thickness of tissue afford the pathways for the development of the fibrillary circuits which sustain the fibrillary state.

SUMMARY

Auricular fibrillation of the fleeting type occurring in an infant with signs of congenital heart disease was followed from the age of 2 months to its fatal termination seven months later. Digitalis was only partially effective in controlling the ventricular rate. Auricular fibrillation in the newborn infant is rare, only one other instance having been reported in the literature. This case differed from ours in that the fibrillation was continuous and was controlled by digitalis.

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EXTREME PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

CASE REPORT

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PAROXYSMAL supraventricular tachycardia is a condition in which the heart beats rapidly and regularly in response to impulses arising in the auricles or above the bundle of His. The usual episodes are characterized by abrupt transitions from normal rhythm to tachycardia at their onset and from tachycardia to normal rhythm at their termination. These attacks seldom last over a few hours and at the most from five to six days. The heart rate is usually between 150 and 250 a minute; faster rates do occur but are rare because the ventricles are unable to respond to stimuli from the auricles over 300 a minute. Edeiken,¹ in a review of the literature, found that the upper limit at which the ventricles of the adult human heart can beat for a relatively prolonged period is about 300 a minute, although in infancy several cases with a higher rate have been recorded.

A study of our electrocardiographic files over the past ten years did not reveal any tachycardias at this faster rate and, as only seventeen cases have been recorded in the literature, we are presenting this additional report.

CASE REPORT

A 7½-month-old white infant was admitted to the Medical College Hospital on April 23, 1945. The child had been normal in every respect up to April 14, 1945, when he became fretful and restless and developed a slight cough and rectal temperature of 102° F. He was given antipyretic powders but continued to cough and had some difficulty in breathing, with no cyanosis. On April 20 he was given small doses of sulfadiazine. The morning of April 22 the infant's heart rate was 180 and, as he continued to be listless and the tachycardia persisted, the parents brought the child to the hospital on the night of April 23.

Examination.—The baby was well nourished and weighed 16 pounds, 13 ounces. The temperature was 101° F., respiration 40. There was no cyanosis. He was restless but took nourishment well without regurgitation. The neck veins were moderately distended and a few coarse ronchi were heard in the lung bases. The heart sounds were extremely rapid and trip hammer in quality. There were no murmurs. The apical rate was difficult to count but was well over 280 per minute. The liver edge was palpated two fingerbreadths below the right costal margin. There was no peripheral edema.

Laboratory Data.—The urine was acid, with 2 plus albumin, negative sugar, and a normal sediment. The red blood count was 3,610,000, with a hemoglobin of 73 per cent Sahli. The white blood count was 13,000, with 39 polymorphonuclear neutrophile leucocytes, 1 eosinophile, 58 lymphocytes, 1 normoblast, and 2 endothelial cells. The Wassermann was negative.

X-ray of the chest showed the transverse of the heart to be 9.4 cm., transverse of the thorax 15.2 cm.; the cardiothoracic ratio was 62 per cent. The left side of the heart was enlarged and there was a slight increase in the hilar lung markings.

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The electrocardiogram on April 24, 1945, showed a supraventricular tachycardia, with a ventricular rate of 300 per minute. A second tracing after digitalization, on April 26, 1945, showed a regular rhythm, with a ventricular rate of 136.

Clinical Course.—While in the hospital, the infant was restless and fretful but continued to take nourishment. Carotid sinus pressure had no effect on the tachycardia. Intramuscular digitalis was started, in 0.25 cat unit dosages, and continued for twenty hours. During this time, 2.5 cat units were given; twenty-one hours after the last dose the heart rate returned to normal. No further medication was given, but after forty-eight hours the tachycardia recurred, lasting for several hours. The venous engorgement and liver enlargement disappeared after the rate slowed to 136 per minute.

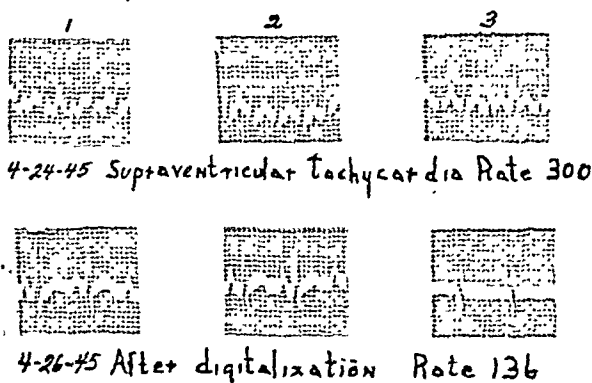


Fig. 1.—Extreme supraventricular tachycardia before and after digitalization.

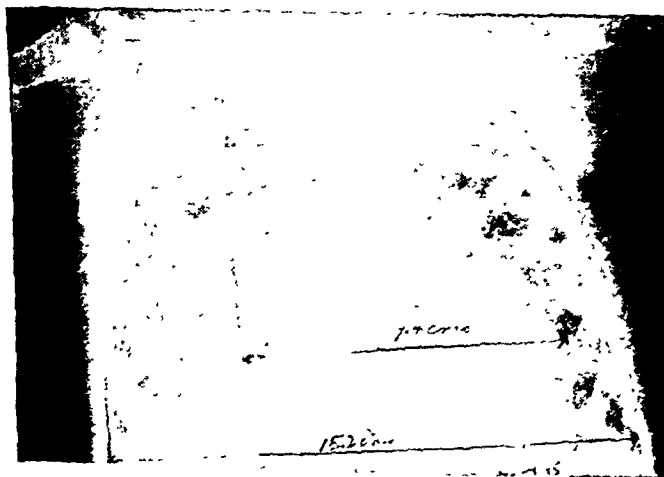


Fig. 2.—Roentgenogram of the chest showing diffuse cardiac enlargement, cardiothoracic ratio 62 per cent.

The child was discharged six days after admission but, after several days at home, the tachycardia returned. The child was then taken to Johns Hopkins Hospital and seen by Dr. Helen Taussig. At that time the digitalis was repeated and in a few days the tachycardia disappeared.

The infant has been continued on eight drops of tincture of digitalis since then and was seen by one of us (E. L. K.) on June 1, 1945. The child seemed perfectly normal and had gained a pound. The heart rate was 136 and an electrocardiogram was similar in every respect to our last tracing.

DISCUSSION

We believe that a distinction should be made between supraventricular tachycardia occurring in a damaged heart, tachycardia with the usual rates, and extreme tachycardia. The first type may be very dangerous, because a damaged heart is unable to withstand any excess strain. Therefore, an attempt should be made to halt the tachycardia immediately. The drugs of choice in an adult are quinidine, digitalis, mecholyl, or magnesium sulphate. Frequently, carotid sinus pressure, ocular pressure, or gagging, will terminate an attack, but if these procedures fail, one is justified in using quinidine, preferably by mouth. The dosage is usually 3 grains given three times daily. This may gradually be increased and at times 15 grains three times daily may be required to halt an attack. This drug is not without danger and fatalities have been reported from its use. Digitalis will frequently terminate an attack, but should be used in full therapeutic doses. Mecholyl is a powerful parasympathetic drug and must be given subcutaneously in adult dose of from 10 to 25 mg.; probably a 2 to 5 mg. dose would be adequate in a child. The ill effects of mecholyl may be abolished very quickly by intramuscular atropine, so it is always wise to have atropine ready for use when mecholyl is given. Magnesium sulphate has been successful in causing a cessation of supraventricular tachycardia. It is used in 1 Gm. doses intravenously in adults and much smaller doses intramuscularly might be advocated in children. If the heart has not been previously damaged, the usual supraventricular tachycardias will respond to this treatment very promptly, and there is seldom any need for continuing treatment, as these individuals have normal hearts which do not seem to be embarrassed by an episode of tachycardia.

Extreme tachycardias apparently lie in a different category. They have been discovered more often in children and have seldom been associated with organic cardiac disease. It is doubtful whether the parasympathetic nervous system functions in very young children and certainly we should hesitate in using toxic cardiac drugs on these infants. Digitalis is probably the least harmful of these drugs. Quinidine might be used orally in small doses, but we should hesitate to advocate either mecholyl or magnesium sulphate. It is our belief that if a physician would have courage enough to withhold medication for an attack, it probably would terminate without the use of any drug, as the ectopic focus would finally become fatigued and allow the sinoauricular node to take over its normal function.

The extreme tachycardia in this infant lasted four days and afterwards there were several recurrences. Although cardiac dilatation is an uncommon complication in paroxysmal tachycardia (Levine²), it did occur in our case. All of us who saw this infant were convinced that he did not have intrinsic cardiac disease, but it is quite possible that cardiac weakness might develop later, on account of the terrific strain on the myocardium.

Edeiken¹ concluded that drug therapy had very little effect on any of the previously reported cases and we must admit that in our case the tachycardia did not terminate until twenty-one hours after the last dose of digitalis. One might assume that there was a cumulative effect, but as the drug was given intramuscularly, it should have terminated the attack much earlier. We believe that there is very little indication for the continuance of digitalis in patients who have suffered attacks of tachycardia. It would seem better to use drugs during an attack, rather than attempt to prevent the attack.

SUMMARY

Extreme supraventricular tachycardia is probably not as rare as it would appear from the literature. Many cases are probably not discovered because of their sudden onset and spontaneous termination. The treatment of choice in infants is digitalis, but prognosis is good if there is no underlying cardiac disease.

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CORONARY THROMBOSIS

REPORT OF A CASE IN AN INFANT ELEVEN MONTHS OF AGE

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A REVIEW of the literature reveals that coronary thrombosis in infancy is extremely rare. Coronary thrombosis has been reported by Hughes and Perry¹ (1929) in an infant 7 weeks of age and Ramsey and Crumrine² (1931) in an infant 4 months of age.

It is the purpose of this communication to record a case of coronary thrombosis in an infant 11 months of age.

CASE REPORT

History.—D. P., an 11-month-old male infant, was admitted to the Children's Free Hospital of Louisville, Ky., August 18, 1944, with the chief complaints of vomiting, cyanosis, and irritability. The child had been irritable for the past two weeks, especially at night, and had vomited and refused food for two days prior to admission. Intermittent cyanosis developed the day before admission.

Past history revealed that the delivery was normal; he had been admitted to the General Hospital, March 19, 1944, with diarrhea, otitis media, stiff neck, and a rash of two days' duration. Physical examination at that time revealed the following: dry lips, flaccid left leg, generalized erythematous rash, enlarged cervical nodes, reddened left tympanic membrane, and weight of 16 pounds.

Laboratory studies at that time showed the following: Roentgenograms of long bones, skull, and chest were negative; spinal fluid revealed sugar, 66.6 mg. per cent, protein 70 mg. per cent, chlorides 742 mg. per cent, and a cell count of 12 lymphocytes. Blood, stool, and throat cultures, tuberculin, Schick, Kahn, urinalysis, and agglutinations for typhoid, paratyphoid A and B were all negative. The white blood cells ranged from 12,250 to 8,750 cells per cubic millimeter and red cells from 4,060,000 to 3,590,000 per cubic millimeter with a hemoglobin of 10.5 Gm. per 100 c.c. of blood. The electroencephalogram was interpreted as abnormal for an infant because of the lack of any fast wave forms and low frequency high voltage delta waves in the occiput. There also was evidence that visual stimulation did influence the occipital wave form.

The infant remained in the hospital for a period of thirty-six days, lost weight, and ran a spiking type of temperature for three weeks. Treatment consisted of sulfathiazole, sulfadiazine, ear irrigations, buttermilk, vitamins, and transfusions of whole blood and plasma. Schilder's disease was considered, but he was discharged April 24, 1944, with a diagnosis of toxic encephalitis, nonspecific diarrhea, and left otitis media.

He was seen periodically in the Out-Patient Clinic up to May 29, 1944, at which time he had gained to 16 pounds. He was still unable to sit alone.

The family history revealed that the mother had several convulsions during the gestation period. There were six siblings living and well.

Physical Examination.—On admission to the hospital August 18, 1944, the physical examination revealed a well-developed and well-nourished white male, who was very restless and cyanotic. Respirations were rapid and breath sounds were exaggerated, but no râles could be heard. The heart rate was regular and no murmurs could be detected. The lower

From Department of Pediatrics, services of Drs. James W. Bruce and W. W. Nicholson and Department of Pathology, University of Louisville School of Medicine.

extremities were flaccid and the deep reflexes were sluggish to absent. There was marked weakness of the back and the infant was unable to sit alone. The temperature was 99.4° F. and the weight was 17 pounds, and 14 ounces. The clinical impression was bronchopneumonia.

Laboratory.—The initial white blood cell count was 24,600 per cubic millimeter with a differential of polymorphonuclear leucocytes 70 per cent and lymphocytes 30 per cent.

Course and Treatment.—The infant was immediately placed in a continuous oxygen tent and 10,000 units of penicillin were given intramuscularly. One and one quarter hours following admission the child became cyanotic, started crying and gasping for breath. Despite all emergency measures the infant expired ten minutes later.

Post-Mortem Examination.—The pericardial cavity was entirely obliterated by dense fibrous adhesions. The heart was enlarged to three times normal size and weighed 130 grams. As the pericardium was dissected away from the epicardium there were large firm prominences noted in the region of the atrioventricular sulcus and these were found to be markedly enlarged coronary vessels. On cut section the vessels were enlarged to as much as one centimeter in diameter but having a lumen that barely admitted a fine probe. These changes involved the proximal portion of the right coronary artery and ended abruptly at a point where the vessel turned downward to become the posterior descending branch. The transverse branch and also the left marginal artery of the left coronary system were involved. Dissection of these vessels revealed them to be thrombosed with rather old blood which had undergone considerable organization.



Fig. 1.—Section of the left coronary artery.

The lungs were edematous and one and one-half times their normal weight and had many petechial hemorrhages on the pleural surfaces.

The liver weighed 240 grams and displayed marked venous congestion.

Unfortunately permission for head examination was not obtained.

Microscopy.—There was marked inflammatory reaction in both the pericardium and epicardium. Sections of the heart muscle revealed rather marked fibrosis and in one of the sections there was recent hemorrhage and necrosis which had the appearance of recent infarction. The coronary vessels were markedly enlarged because of dilatation and hyperplasia involving chiefly the intimal coat. In some sections all layers were hypertrophied with calcification at the periphery, in others there was necrosis of the media and adventitia, not unlike periarteritis nodosa. Many of the badly damaged vessels were occluded by inti-

mal thickening but had recanalized; in others the lumina were almost completely obliterated by thrombosis which had apparently been present for some time. The left coronary artery appeared to be completely occluded (Fig. 1*) resulting in an infarction seen in the myocardium.

The lungs revealed edema and vascular congestion and in some areas showed recent hemorrhage into the lung parenchyma.

The hilus lymph nodes contained caseous tubercles.

The pancreas revealed marked hyperplasia of one of the medium-sized arteries, but thorough examination of all other tissues failed to reveal any similar lesions.

COMMENT

Death in this child was due to coronary thrombosis. The lesions found in the coronary vessels and in one vessel of the pancreas were not unlike periarteritis nodosa but the changes in the vessel walls and the thrombosis were more suggestive of thromboarteritis obliterans.

CONCLUSION

Coronary thrombosis in an 11-month-old infant, with post-mortem findings, is herein reported.

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*Photography by Mr. W. L. Williams.

PNEUMOCOCCIC STOMATITIS

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THAT THE pneumococcus appears growing in the pharynx is a fact recorded by the textbooks. Pneumococci growing primarily in the mouth is not generally recognized, or, if the condition is observed, the cases have not appeared in the literature. Crawford¹ recorded nine cases which he had observed. These were the only cases it was possible to find recorded in the literature during the past twenty years. Textbooks on pediatrics, and on diseases of the mouth do not apparently recognize the condition, although Griffith and Mitchell² state that a pseudomembrane may be produced in the mouth by the pneumococcus, perhaps in the course of pneumonia. It is possible that cases of pneumococcic stomatitis may be appearing unrecognized. If the condition is as unusual as is indicated by the textbooks and the literature, the report of this case seems indicated.

A male infant, 5 weeks of age, was first seen in the Out-Patient Department of the Army Air Forces Regional and Convalescent Hospital at Coral Gables, Fla., Jan. 16, 1945. The mother stated that the child had been well until Jan. 2, 1945, when she first noticed that he began to be irritable and to refuse his formula. It was at this time that she observed white patches in his mouth which she assumed to be particles of milk. The patient was seen by a local physician who applied gentian violet to the mouth. The mouth appeared to clear and the child seemed well within a few days. On Jan. 9, 1945, the mother again noticed white patches in the mouth, but in spite of repeated applications of the gentian violet the mouth became gradually worse. At the time of his first visit the baby appeared to be normal in every way excepting for the lesions in the mouth.

The lesions were located on the buccal mucous membranes, on the gums, both above and below, on the tongue margin, and beneath the tongue. The membrane was thin, translucent, and was firmly adherent. The mucous membranes bled freely when the membrane was removed. There was no induration of the surrounding mucous membrane. There was no detectable odor. A smear made for Vincent's organisms was negative. It was assumed that this was probably a severe stomatitis due to thrush, and the mother was directed to intensify the gentian violet treatments and to return to the clinic in two days.

The baby was seen again Jan. 18, 1945. The mouth infection had become worse and the child was very irritable. He was admitted to the Jackson Memorial Hospital, military dependents' service. Penicillin, 250 units to the cubic centimeter, was applied locally every two hours in addition to the gentian violet. The following day, Jan. 19, 1945, the baby appeared to be worse. There was a quantity of mucus in the pharynx and he was coughing. It was feared that he might be developing a pneumonia although the chest remained clear. A smear of the membrane taken from the mouth failed to demonstrate any organisms. There were numerous, large squamous epithelial cells, and an occasional pus cell. The blood count taken at that time showed red blood cells 3.2; hemoglobin, 10.8 Gm., white blood cells, 7,950. The differential: stabs 2, segmented cells 16, total neutrophils 21, lymphocytes 74, monocytes 2, eosinophiles 2. Penicillin therapy was begun; 3,000 units per cubic centimeter were given intramuscularly every three hours. The patient appeared to be critically ill and for that reason sulfadiazine, grains 1 per pound daily, was also given.

On January 20, there was no improvement. The breathing was more labored. The membrane in the mouth showed no change. X-ray of the chest showed no pathology to be present. The urine was normal. The culture taken from the membrane in the mouth January 18 was reported type XIV pneumococcus.

On January 21, the patient was apparently having tracheobronchitis, so that oxygen was administered. Atropine was given in an attempt to reduce the amount of secretion from the mouth. The membrane in the mouth persisted unchanged.

On January 22, the second culture from the membrane in the mouth was reported as type XIV pneumococcus, this time with a staphylococci contaminant. The blood count showed red blood cells 3.3, hemoglobin 10.8 Gm., white blood cells 12,700. Differential: neutrophils 61, lymphocytes 35, monocytes 2, and eosinophiles 2.

There was a definite difference in the appearance of the membrane in the mouth on January 24. The membrane, which had formerly been thin, now became thicker. It was beginning to free itself from the margins and was friable. The general appearance of the patient was much improved. The respirations were no longer labored and he began to take his formula.

On January 27, the membrane had cleared from the mouth and medication was discontinued. He had received a total of 165,000 units of penicillin intramuscularly. He was discharged from the hospital Feb. 3, 1945, apparently recovered.

Smears and cultures were taken from the nasopharynxes of the mother and two grandmothers, the only people who had contact with the patient. These were reported negative for pneumococci.

The temperature of the patient at no time exceeded 101° F. A membrane was never observed in the pharynx.

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RIGHT-SIDED TRANSIENT PARALYSIS OF THE DIAPHRAGM IN A NEWBORN INFANT

CASE REPORT

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THE occurrence in the New Born Service at the Jewish Hospital of the first recognized case of isolated phrenic nerve injury with paralysis of the diaphragm merits a report since it is the eighth such recorded case. Paralysis of the diaphragm associated with brachial paralysis in newborn infants is likewise a rare condition—approximately twenty-five cases having been recorded to date. Zeligs,¹ in 1928, described the first case seen in Cincinnati. Diaphragmatic paralysis has been recognized since 1902, when Naunyn² reported the first case. Since then others³ have reported occasional cases, but Kofferath⁴ was the first to study an infant with paralysis of the diaphragm by means of the fluoroscope. He described the paradoxical movement of the affected diaphragm and showed that it was necessary to use fluoroscopy to rule out other pathologic conditions, which might be confusing if only a flat plate of the chest were taken and elevation of the diaphragm found. Their chief conditions to be differentiated are; intracranial hemorrhage, empyema, atelectasis, diaphragmatic hernia, and pneumonia. Congenital heart disease is also ruled out as to the cause of cyanosis and respiratory difficulty by the fact that fluoroscopic examination shows normal cardiac configuration and pulsations. Blattner,⁵ in reviewing the six cases of unilateral diaphragmatic paralysis without brachial palsy reported previous to his, found that in four the diaphragm was paralyzed on the right side; whereas, it was paralyzed on the left side in the other two cases. In his own case, the right side of the diaphragm was paralyzed. His report is the most completely worked-up case—the only one with microscopic pathologic findings on the phrenic nerves. Degeneration of the phrenic nerve and of the muscle fibers of the diaphragm were the principal pathologic findings. Following the idea of Rupilius⁶ Blattner believes that prenatal compression of the phrenic nerve due to the position of the fetus in utero during the last months of pregnancy, rather than obstetric manipulation, is the cause of this condition. He also stresses the importance of fluoroscopic examination in all newborn infants showing respiratory distress. The diagnosis was made of his patient at the age of 4 months. In the other six cases reviewed by him none of the patients showed symptoms at birth, the earliest symptoms appearing the third day. In our case symptoms began on the fourth day and fluoroscopic examination made on the seventh day disclosed a right-sided diaphragmatic paralysis.

CASE REPORT*

R. L. T. (Case No. 44-7739), a male infant, was born at the Jewish Hospital on Oct. 29, 1944, at 12:35 A.M., of a tall slender primipara with a small pelvis. The labor was

From the New Born Service and Roentgen Ray Department of the Jewish Hospital.
*Kindness of Dr. Frank J. Albers.

within normal limits, lasting eight hours. Pitocin was given at 12:06 A.M. and low forceps with good application to the head in a L. O. A. position were used with the patient under gas, oxygen, and ether anesthesia which was given for twenty-five minutes.

The infant was resuscitated with some difficulty, but after oxygen was given and a large amount of mucus was aspirated from the throat the baby cried well and was sent to the nursery in good condition. He weighed 9 pounds, 14 ounces. The baby did well for the first three days, nothing unusual being noticed by the nurses or physicians. He nursed at the breast and took the bottle containing complementary feedings well. On the fourth day (Nov. 1, 1944) it was noticed that the baby had some difficulty with his breathing and did not take his feedings well. Tentative diagnoses of intracranial hemorrhage or congenital heart disease were made due to the appearance of cyanosis on Nov. 3, 1944. One of us (J. V. G.) was requested to see the baby on Nov. 4, 1944, the seventh day of life. The infant vomited that day for the only time during his entire stay in the nursery.



Fig. 1.—Roentgenogram (Nov. 4, 1944) showing elevation of right diaphragm.

Examination revealed a somewhat cyanotic, but well developed and well-nourished, full-term, male infant lying on his back and breathing with difficulty. However, he cried well and resisted examination. The head had a caput succedaneum in the right occipital region. The pulse was 150 and the respirations were about 70 per minute. All extremities were normal. No paralysis was present. The fontanelles were level and of normal tension. The eyes, ears, throat, neck, abdomen, genitals, and the skin, except for cyanosis, were negative. The chief abnormal signs were in the chest. The respirations were rapid, thoracic in type and labored. The left chest moved in an exaggerated manner in contrast to the right side, which was relatively quiet. There was normal resonance throughout the left side with normal breath sounds. The right side showed impaired resonance throughout the back with diminished to absent breath sounds. The heart was rapid and a systolic murmur was present at the apex. There was no elevation of temperature at any time. A tentative diagnosis of atelectasis on the right side was made. A roentgenogram was ordered and a fluoroscopic examination was made at once. The fluoroscopic examination showed that the

baby was breathing only with the left side of the chest—the right side being practically immobile. At each respiration the mediastinum moved in a to-and-fro direction as a result of the paradoxical or see-saw movement of the diaphragm—the left side going down with inspiration while the right side, although appearing to be relatively fixed, raised a little during inspiration. The heart was displaced to the left and downward by the mediastinal shift, but the contour was normal. The roentgenogram (Fig. 1) confirmed the high diaphragm at the level of the fifth rib on the right side. In fact, there was a heated discussion, when this case report was made before the Staff Conference, particularly about the diagnosis of the roentgenogram. Several opinions were expressed that the diagnosis was simply atelectasis with the negative pressure in the right chest producing a high position of the diaphragm. As already stated, the diagnosis of diaphragmatic paralysis can only be suspected as one of several possibilities by a study of the flat plate of the chest; the final differentiation must be made by observing the infant under the fluoroscope. The diagnosis of paralysis of the right diaphragm was made and treatment was instituted at once.

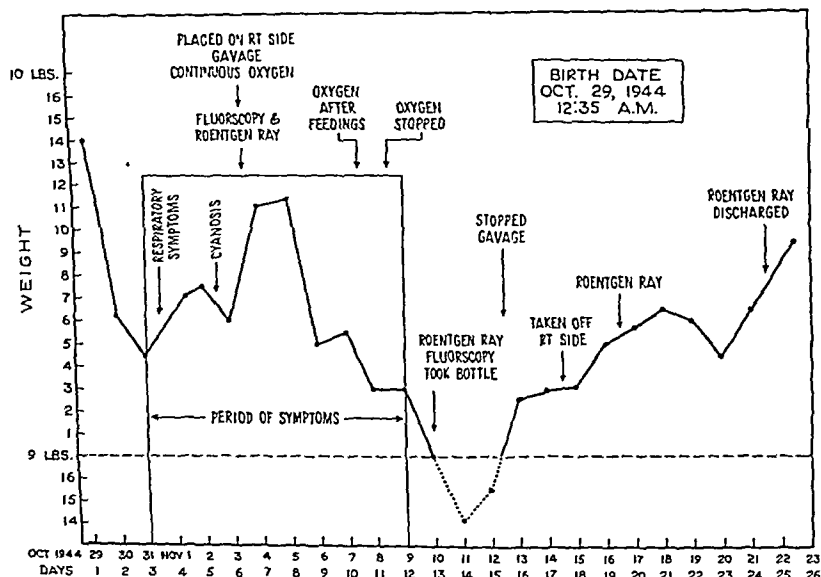


Fig. 2.—Weight chart and pertinent clinical data.

Treatment.—The infant was placed on the right side to splint it, oxygen was started continuously and gavage feedings were given. The cyanosis and respiratory distress were relieved to a surprising extent. The breathing became quiet and the heart rate decreased. The systolic murmur and the dullness of the right chest disappeared, while the breath sounds were heard equally throughout both lungs. However, the infant's respiration became embarrassed whenever he was taken off of his right side. Although there was some loss of weight for a few days, steady improvement began (weight chart Fig. 2). The stools were normal at all times and in two days the baby began to take the bottle again. Continuous oxygen was stopped and was administered only after feedings; it was discontinued entirely on Nov. 9, 1944—nine days after onset of symptoms.

A second roentgen ray and fluoroscopic examination on Nov. 11, 1944, showed definite increase in the movement of the right diaphragm and better aeration of the right lung. It was possible to place the baby on the back and left side for an increasing length of time on Nov. 14, 1944, without respiratory distress.

A third roentgen ray examination on Nov. 16, 1944 (Fig. 3), showed the condition to be practically normal and the baby was discharged in good condition on the twenty-sixth day (Nov. 26, 1944). The baby weighed 9½ pounds when discharged; this

was four ounces under the birth weight of 9 pounds, 14 ounces. After discharge to the home, he began immediately to show a normal weight gain. He has continued to do well and has been seen on Nov. 29, 1944, Jan. 12, 1945, Mar. 20, 1945, and on April 16, 1945, at which time fluoroscopic and roentgen ray examination showed a normally functioning diaphragm with no mediastinal shift and the heart in normal position. The baby was in excellent condition and breathed normally. When last seen at the age of 5 months, he weighed 15 pounds, 4 ounces.



Fig. 3.—Roentgenogram (Nov. 16, 1944) showing normal position of right diaphragm. Baby's body rotated producing distorted position of heart.

DISCUSSION

In discussing this case and phrenic nerve paralysis of newborn infants in general, we wish to emphasize the following points: Although the condition is rare as far as reported cases are concerned, it can be justifiably deduced, as expressed by Friedman and Chamberlain,⁷ that "Phrenic nerve injury in the newborn cannot be so unusual an occurrence when we take into account the intimate relationship of this nerve to the brachial plexus. It is a reasonable assumption that any serious injury to the upper cord of this plexus is likely to involve in some measure the filaments that make up the phrenic nerve." It also seems reasonable to assume that the phrenic nerve can be injured without involvement of the brachial plexus. Kofferath, likewise expresses the belief that this type of injury is not very rare, especially when associated with Erb's palsy. It is almost invariably overlooked probably because cyanosis, the most prominent symptom it gives rise to, is common to numerous pathologic conditions frequently encountered in newborn infants.

It is suggested that phrenic nerve paralysis should be excluded in every case of brachial palsy. Furthermore, one should not fail to consider this condition in the differential diagnosis when the newborn baby displays cyanosis, irregular, labored, or accelerated breathing, unilateral diminution of breath sounds with or without moisture, or unaccountable gastric disturbances. When there is doubt, the infant should be fluoroscoped, for, when the possibility of the occurrence of diaphragmatic paralysis is once appreciated, its discovery is usually accomplished with ease.

SUMMARY

A case of transient paralysis of the right side of the diaphragm due to so-called isolated phrenic nerve injury in a newborn infant is reported. Signs of respiratory distress and cyanosis appeared on the fourth day of life. The diagnosis was made on the seventh day by means of fluoroscopy.

The relatively prompt relief of the symptoms with restoration of the function of the diaphragm nine days after symptoms began, and six days after institution of treatment, showed the transient nature of the phrenic nerve injury in this case. Regeneration of the injured nerve sufficient to allow normal impulses to the diaphragm was undoubtedly made possible by resting of the nerve through the method of treatment used which consisted of placing the infant on the right side to splint it and by giving continuous oxygen and gavage feedings. This case has the shortest duration on record of acute symptoms and signs commonly associated with diaphragmatic paralysis; and is the first one in which the described methods of treatment are reported.

This is the first recognized case of diaphragmatic paralysis in the New Born Service of the Jewish Hospital and is the eighth recorded case without accompanying brachial paralysis.

It is a pleasure to express our appreciation to Miss Billie Ann Craven, supervisor, of the New Born Service, and her corps of nurses and nurses' aides, for their intense interest in this unusual case. The constant care of this splendid group of women was, in our opinion, the largest factor in the rapid improvement and final recovery of this infant.

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LEPTOMENINGEAL CYST ASSOCIATED WITH HEMIPLEGIA AND SKULL DEFECT OF TRAUMATIC ORIGIN

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MARQUETTE, MICH.

AMONG the variable complications that follow severe craniocerebral trauma, the development of the syndrome of leptomeningeal cyst, hemiplegia, and skull defect is of relatively infrequent occurrence. Apparently, because of the striking roentgenologic features present, this condition has more sharply excited the attention and interest of roentgenologists. Dyke,¹ for example, not only presented a clear description of the roentgenologic changes, but also offered an explanation of the manner in which these changes take place. Since this condition occurs as frequently in children as in adults, the pediatrician, as a member of a clinical team, may find himself in a position of usefulness relating to the factors of diagnosis and decisions arising as to proper therapeutic management.

Leptomeningeal cysts are produced by severe head trauma invariably accompanied by skull fracture usually of the comminuted or depressed variety. They develop as the result of laceration of the arachnoid, pia mater, and, in many cases, the dura mater as well. Dyke believes that while hemorrhage may play an important role in the formation of these cysts, actually the areas of the subarachnoid space become separated from the general subarachnoid space in the process of healing of the lacerated membrane, forming cystic collections of fluid. The skull defect develops as a result of resorption of bone overlying the cyst and is brought about by the pulsating pressure of the brain, much in the same way in which bone resorption is produced by aortic aneurysms in their proximity to such bony structures as the sternum, ribs, and vertebrae. The neurologic changes result from destruction of the regional cortical tissue of the brain.

The following case report covers a ten-year period of observation of a patient from the time of her head injury to that of operation, thereby offering an unusual opportunity for study of the clinical aspects of this condition over a long period of time.

REPORT OF CASE

J. J., a 5-month-old girl infant, was admitted to the hospital on Aug. 1, 1933, five hours after an accident in which an aunt had fallen down a flight of stairs while carrying the baby. The patient was born at term, weighing $8\frac{1}{2}$ pounds. She had been progressing satisfactorily, although it was thought that she was rather pale previous to her accident. Drowsiness, vomiting, and pallor were noted in the infant soon after the accident. Initial examination when the child was brought to the hospital revealed a blanched, semi-comatose infant, irritable when aroused. There was asymmetry of the skull produced by a soft swelling on the right side of the head extending from the anterior parietal area to the occiput. The skull underneath the swelling could not be satisfactorily palpated. There was

From the Northern Michigan Children's Clinic.

no evidence of bleeding from the various external orifices. No evidence of paralysis was made out at this time. No cranial nerve palsies or pathologic reflexes were detected. The hemoglobin was 60 per cent and the red blood count, 3,100,000. Roentgen examination confirmed the admission impression of skull fracture involving the right parietal bone.

The patient was treated conservatively with magnesium sulfate rectally and hypertonic glucose solution intravenously. Within twenty-four hours, the patient recovered from the initial shock symptoms and was able to nurse at the breast. She continued to improve rapidly thereafter and was discharged on the eighth hospital day. The day before her discharge, her hemoglobin was 65 per cent and her red blood count, 3,450,000.

Subsequent Course.—One week following discharge from the hospital, the swelling on the right side of the head had become considerably reduced in size. Aspiration of the mass yielded 15 c.c. of thin, hemorrhagic fluid. The hemoglobin had risen to 70 per cent and the red blood count to 3,820,000.

The patient was seen at frequent intervals over the next two years (1933 and 1934). The fluctuant mass over the right parietal area gradually decreased in size during this time. Definite increase in the tension of the mass could be made out when the patient cried, indicating the presence of its communication with the ventricular system. At the age of 7 months, weakness of the left arm was detected and at 11 months, weakness of the left leg with slight spasticity of both the left arm and leg became apparent. There was no associated facial paralysis. She learned to walk at 15 months. Her gait appeared to be hemiplegic in type. Spasticity of the left arm and leg became more marked and the gait more characteristically hemiplegic during the following two years (1935 and 1936). During this time, physiotherapeutic treatment was carried out. The swelling over the right parietal area had disappeared, revealing a large, palpable bony defect in the skull. With the ensuing years, moderate atrophy of the left arm and leg developed, the atrophy of the left arm being more pronounced than that of the leg. The shortening of the leg was sufficient to produce a limp of moderate degree together with a compensating curvature of the spine. There was no impairment of intelligence; in fact, she was an honor student in school.

In 1941, the question of operation presented itself when the diagnosis of leptomeningeal cyst was entertained. Because of the excellent mental status of the child and the doubt at the time as to the ultimate benefit offered by surgery, the matter of surgery was left in abeyance. The question of surgery was again considered two years later from the point of view of closing the skull defect with tantalum, in addition to the possible beneficial results to be obtained by removing any existing cystic structure. This course was decided upon and operation was performed (Jan. 24, 1944) by Dr. Max Peet, Head of the Department of Neurosurgery of the University Hospital, Ann Arbor, Mich., with whom the problem was discussed.

Summary of Operative Findings.—When the skin flap overlying the skull defect was reflected and dissected free, the defect was found to extend from the midline down toward the right ear for a distance of approximately 11 cm., measuring 5 cm. in width. The edges of the skull defect which were depressed were removed with the aid of the rongeur. A leptomeningeal cystic structure was opened and approximately 10 c.c. of fluid were removed. The cystic mass seemed to be made up of several cysts measuring from 0.5 cm. to 0.7 cm. The cortex of the underlying brain appeared to be destroyed for a depth of 2.0 cm. Scar tissue present in this area was removed, in the process of which a piece of detached bone was found and extracted. Another bone fragment was found inside of the longitudinal sinus. This was also removed. The bony defect was closed with a tantalum plate.

Summary of the Roentgenologic Findings.—Studies of the skull on the day of admission to the hospital (August 1, 1933) showed the presence of a fracture extending from the sagittal suture into the mid-portion of the right parietal bone (Fig. 1.). Also present in this area were less prominent linear fractures. There was a suggestion of the presence of a transverse fracture through the occipital squama. The presence of a depressed fracture in this film was not definitely apparent.

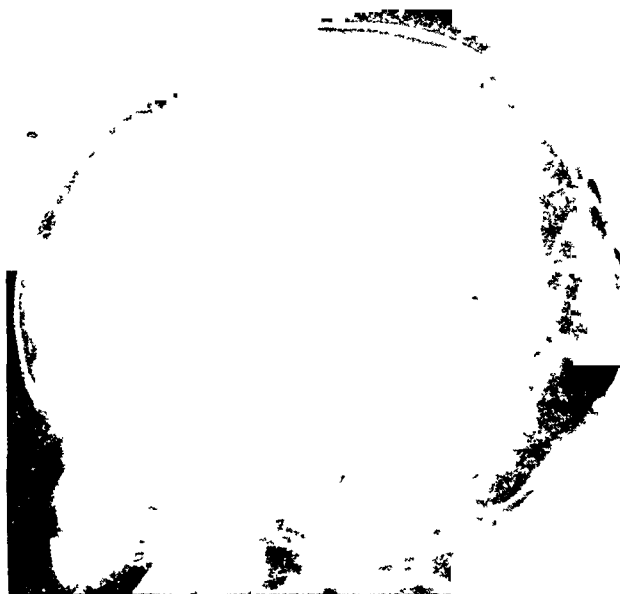


Fig 1—Admission roentgenogram (Aug. 1, 1933) showing a fracture extending from the sagittal suture into the mid-portion of the right parietal bone



Fig 2—Illustrating the development of a large area of bone resorption in the area of the skull fracture four and one-half months after the accident (Dec. 15, 1933), made up of circumscribed areas of rarefaction with sclerotic changes at their margins, a scalloping effect produced in the inner table of the skull by the pressure of the leptomeningeal cyst

By four and one-half months (Dec. 15, 1933), a large area of bone resorption had appeared roentgenologically, made up of circumscribed areas of rarefaction with slight sclerotic changes at their margins (Fig. 2.) corresponding to the scalloping effect of the inner table of the skull described by Dyke, produced by the presence of underlying cystic structure.

Roentgenograms of the skull obtained periodically over the ensuing years showed persistent failure of closure of the defect. There was suggestion of a disturbance of ossification as evidenced by the irregularly increased thickening of the skull in the involved area (Fig. 3.).



Fig. 3.—Roentgenogram taken eight years after the accident (Aug. 9, 1939) showing more striking development of the skull defect, the roentgenologic picture being practically the same at the time of operation, eighteen months later.

COMMENT

The special points of interest in this case, in addition to the recording of an unusual complication of craniocerebral injury, center around the importance of early diagnosis and treatment. Although the development of bone resorption in the area of an earlier, severe skull fracture together with the presence of hemiplegia appears clearly to indicate the formation of a leptomeningeal cyst, a valuable loss of time from the point of view of treatment would seem to be involved if one were to wait for the appearance of bony defect to complete the entire triad. Evidence of a depressed fracture, which commonly accompanies this condition, would doubtless by itself lead to early operative treatment. However, as in the patient here reported, in the absence of definite evidence of a depressed fracture, surgical treatment might be readily overlooked in favor of conservative management. The presence of hemiplegia together with evidence of skull fracture should point to a type of severe craniocerebral injury favorable to the production of a leptomeningeal cyst and thereby call for early surgical inter-

vention. In the case of the patient described here, hemiplegia was not detected at the time of injury; weakness of the arm was detected at two months and that of the leg six months later.* An awareness of its possible presence together with repeated roentgen examinations of the skull for the detection of the skull changes of bone resorption in such cases in young infants will doubtless lead to earlier diagnosis of leptomeningeal cystic formation and to early surgical treatment. Apparently, roentgenologic evidence of bone resorption takes place fairly early. In the patient reported here, such roentgenologic evidence was already well marked four and one-half months after the occurrence of the head injury. Unfortunately, earlier roentgenologic studies following the accident were not performed.

It is probable that an appreciable proportion of such cases occurring in infancy and childhood have gone on to adult life without realization of the true significance of the underlying pathology. Early operative intervention in similar craniocerebral injuries would seem important not only from the point of view of anticipating the development of skull defects, but also with the hope of minimizing the neurologic complications, particularly in patients belonging to the period of rapid growth. It is apparent that had the full significance of the underlying process been recognized earlier and surgical treatment instituted at that time, the patient reported here would have profited in a greater measure.

SUMMARY

An instance is recorded of the development of a leptomeningeal cyst, hemiplegia, and a persistent, large skull defect in a patient who had sustained a severe skull fracture at the age of 5 months and who was observed over a period of ten years.

The skull defect, appearing as a striking feature in this case, made its roentgenologic appearance within a period of several months and was the result of the presence of the underlying leptomeningeal cyst.

Some of the problems of diagnosis and the institution of proper treatment are discussed in the light of the observations in this case.

I am indebted to Dr. Vincent C. Johnson, formerly of the Department of Roentgenology, University of Michigan Hospital, Ann Arbor, Mich., for his interpretation of the roentgenograms.

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BISMUTH NEPHROSIS WITH ANURIA IN AN INFANT

REPORT OF A CASE

DAN P. BOYETTE, M.D.

AHOSKIE, N. C.

REPORTS of the toxic effects of bismuth are not new; many deaths have occurred following its use. The majority of these have occurred in adults who have received repeated doses of the metal or who had received it by accidental intravascular injection. Anuria as a symptom of bismuth toxicity has been reported,^{1, 2} but death due to complete failure of kidney function is uncommon enough to merit mention.

Bismuth, one of the heavy metals, has been used medically for many years, but only recently have the toxic effects been studied.^{1, 3, 4} In general, its pharmacologic action is similar to that of mercury, but the untoward reactions are far less frequent and are usually of a less serious nature. The toxic effects more commonly noted are stomatitis, gastroenteritis, nephrosis, and involvement of the central nervous system. The age and sex of the patient and the form of bismuth administered make no difference in degree of toxicity. The solubility of the preparation is the most influential factor, the more rapidly absorbed ones causing the greater protoplasmic destruction. Oil suspensions are least dangerous, and rapidly absorbable water solutions are most dangerous. Most bismuth compounds, when administered by mouth are not absorbed sufficiently from the gastrointestinal tract to allow the metal to reach any effective level in the blood and tissues.³

It has been shown that bismuth, since it is excreted mainly in the urine, is more toxic to the kidney than to any other organ.⁵ The first effect is that of stimulation, resulting in diuresis, without renal damage being demonstrable. This may be followed by oliguria, then albuminuria, and finally, true nephrosis, at which stage edema and necrosis of the proximal tubules of the kidney can be recognized pathologically.

Complete anuria in an infant as the result of a single injection of a bismuth preparation in the treatment of Vincent's gingivostomatitis is rare. It is felt advisable to warn of the hazards of using such a drug by reporting a case that terminated fatally.

CASE REPORT

R. B., a 2-year-old, 20-pound, female infant, was admitted to the hospital on March 19, 1945, with the history of a "sore mouth" for six days and anuria for thirty-six hours. The local physician had seen the child on the second day of illness, diagnosed Vincent's infection of the mouth, and had prescribed symptomatic and supportive therapy. Because of no improvement in three days, he swabbed the child's mouth with one-half per cent bismuth violet solution and injected intramuscularly one-eighth of the contents of an ampule of this bismol,* a dosage equivalent to 10 mg. of metallic bismuth. Within twenty-four hours

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*Sodium bismuth thiolglycollate, 0.2 Gm., to be dissolved in distilled water.

the child had ceased to void. On the following day (sixth day of illness) the physician catheterized her, but obtained no urine from the bladder. The patient was then referred to this hospital where she was admitted, thirty-six hours after the last urination.

Physical examination revealed an acutely ill infant in semicoma. She could be roused by stimulation but was fretful and irritable. Temperature was 98° F.; pulse rate, 130; respirations, 24; and blood pressure, 118/88. Both eardrums were slightly reddened. The gums and mucous membranes of the mouth were swollen, ulcerated, and bleeding. There was a foul odor to the breath. The bladder and other abdominal organs could not be palpated. Dehydration was not evident. The remainder of the physical examination revealed nothing contributory.

Examination of the blood revealed 12 Gm. hemoglobin, 4.8 million red cells, and 12,000 white cells per cubic millimeter. Blood nonprotein nitrogen was 76 mg. per hundred cubic centimeters and the carbon dioxide combining power was 31 volumes per cent. A smear from the gums revealed fusiform bacilli and spirochetes. Kahn test was negative.

The child was given 200 c.c. of 10 per cent glucose in saline intravenously immediately upon admission, was started on nicotinic acid, 50 mg. three times a day, and the mouth was washed with sodium perborate solution at frequent intervals. Fluids were forced orally. Twelve hours later the child was catheterized; no urine was obtained. A constant drip was then started, and over the next eighteen hours the child received 1,300 c.c. of intravenous fluids. The next morning (third hospital day) the blood chemistry was essentially as on admission. (Chart I.) The child had not voided. Two cubic centimeters of aminophyllin were given intravenously without effect. Six hours later 40 c.c. of 25 per cent glucose with 4 c.c. of aminophyllin were given intravenously. The child continued to be drowsy and was beginning to vomit occasionally.

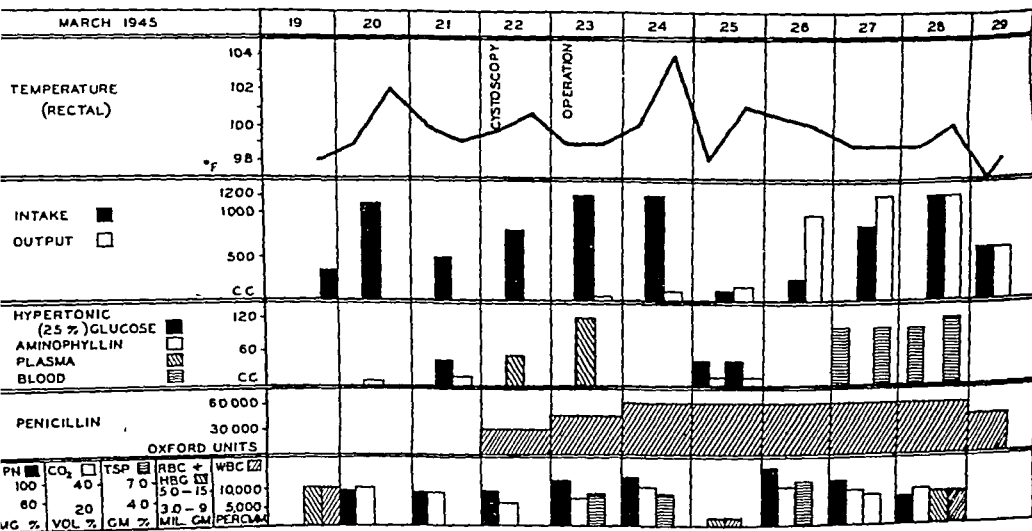


Chart I.

On the fourth hospital day (sixth day of anuria) the patient was cystoscoped and ureteral catheters were passed. A small amount of urine (from 1 to 3 c.c.) was drained from each renal pelvis, but after this was obtained no more flowed from the catheters. This urine contained no cells and was sterile on culture. While the cystoscope was in place, retrograde pyelograms were made, revealing a bifid ureter on the left and a normal ureter and kidney pelvis on the right. Following this she received 500 c.c. of 10 per cent glucose in saline intravenously, and her general condition continued unchanged. Blood nonprotein nitro-

gen remained at the same level. Because of the possibility of the anuria being on an infectious basis, the child was started on penicillin, 5,000 units intramuscularly every two hours.

On the fifth hospital day the patient still had not voided, and her general condition seemed worse. Nitrogenous retention in the blood was increasing. (Chart I.) In view of the seriousness of the situation, decapsulation of the kidneys was deemed advisable. Under ether anesthesia, the kidneys were exposed. A bifid ureter on the left and an aberrant vessel

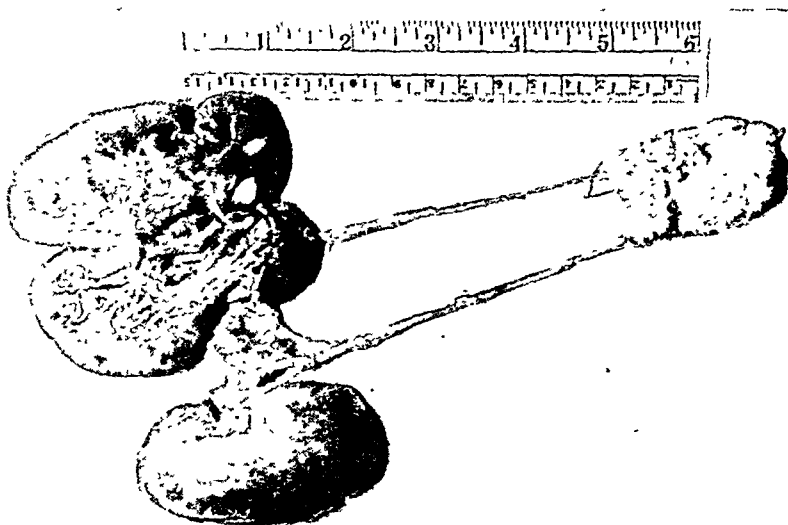


Fig. 1.—The kidneys at post-mortem examination, with the left kidney opened to show the areas of infarction in the lower pole.



Fig. 2.—Photomicrograph of section of kidney showing widespread tubular degeneration ($\times 170$).

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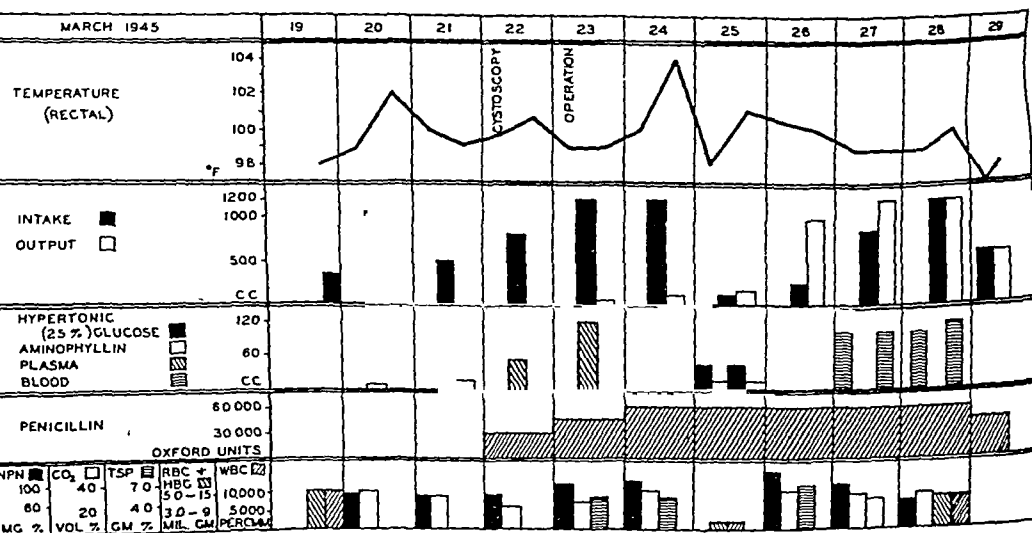


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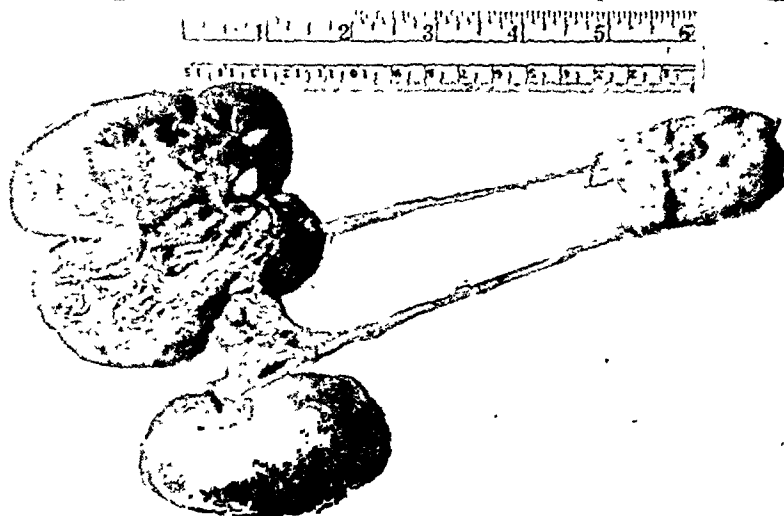


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Fig. 2.—Photomicrograph of section of kidney showing widespread tubular degeneration ($\times 170$).

across the lower pole of the left kidney which almost divided this portion from the main body of the kidney were found. The aberrant vessel was ligated and cut, and the capsules of the kidneys were stripped loose with ease. Over the following twelve hours the child received intravenously 800 c.c. of fluids and 200 c.c. of plasma.

Immediately postoperatively the infant remained essentially as before with the exception that 5 c.c. of grossly bloody urine was obtained from the bladder by catheterization. Fluid intake was maintained by means of the intravenous route and hypertonic glucose solution was injected on two additional occasions. Edema of moderate degree formed in the face and dependent portions of the body. On the fourth postoperative day the infant appeared definitely worse and could be roused only with difficulty. An examination of the blood revealed only 5 Gm. of hemoglobin and 1.6 million red cells per cubic millimeter, with a hematocrit of 14 volumes per cent. Blood nonprotein nitrogen was now 123 mg. per cent, but the other chemistries were in the range of normal (Chart I). Over the following three days four transfusions, totaling 420 c.c. of whole blood, were given intravenously, raising the hemoglobin to 11 Gm. and the red cells to 4.0 million per cubic millimeter. Concurrently with this therapy the infant began voiding small amounts of bloody urine on frequent occasions, and her general appearance was that of improvement.

On the sixth postoperative day (tenth hospital day) the blood nonprotein nitrogen was down to 61 mg. per cent. The infant was taking fluids well orally and was voiding approximately once every four hours. Urinalysis revealed an alkaline specimen with 1 plus albumin, occasional hyaline and granular casts, and an occasional white cell. The edema of the patient was subsiding. It was felt that her general condition was greatly improved and that recovery was assured. However, on the evening of that day she developed a generalized erythematous, petechial, macular rash with generalized increased capillary fragility. The tourniquet test was strongly positive. The abdomen became distended, and the liver edge was palpable four fingerbreadths below the costal margin. The infant presented the picture of one in peripheral vascular collapse. Adrenal cortical extract therapy was begun, but the course was rapidly downhill, and the infant expired on the following day in spite of all supportive measures.

At post-mortem examination confluent areas of ecchymosis were noted over the body and extremities. There was mild edema. The kidneys were pale, but did not appear enlarged; the right organ weighed 70 grams and the left weighed 75 grams. The capsules were absent. A bifid ureter was present on the left, and there was infarction in the lower pole of the left kidney from which the aberrant vessel had been cut (Fig. 1). Microscopically, sections of the kidneys showed mild fragmentation of the glomeruli and lymphocytic infiltration into the interstitial spaces, but the major pathology was widespread tubular degeneration. The tubules were dilated, filled with granular material, and the epithelium was markedly damaged (Fig. 2). In addition, there was congestion of the liver, spleen, and lungs, and pulmonary edema with bronchopneumonia.

Chemical analysis of the renal tissue revealed the presence of 0.5 mg. of bismuth, determined by the method of Sproull and Gettler.⁶ This was 5 per cent of the original amount still present fourteen days after injection and five days after restoration of renal function.

COMMENT

The renal damage in the case presented was a toxic (necrotizing) nephrosis due to the presence of bismuth, as confirmed by chemical analysis. The tubular epithelium was mainly affected with little change in the glomeruli, which is the condition usually found with toxicity due to the heavy metals. It is felt that the aberrant vessel present in this case was of incidental occurrence, and that it played no part in the anuria. The blood in the first urine specimens obtained was, in all probability, due to the trauma associated with decapsulation. When regular flow of urine was re-established, there was a moderate amount of albumin and a few casts, with a small number of cellular elements, which is the condi-

tion one would expect in patients recovering from bismuth nephrosis. This improvement continues over a variable period of time until normal renal function is restored.

Toxic signs other than anuria, such as nausea and vomiting, diarrhea and drowsiness, may or may not be manifest. Uremic symptoms appear if kidney function is not soon restored. Blood pressure may or may not rise and is usually low in the presence of anuria. Edema is uncommon until the late stages.

It should be stressed that care is essential in the administration of bismuth, or any heavy metal, to a child. The urine must be watched carefully, and any deviation from normal should be a signal for discontinuance of the drug. Nephrosis, if it occurs, is best treated by the administration of intravenous fluids and hypertonic glucose solution. Whole blood and plasma are used as indicated to combat anemia and hypoproteinemia. Vasodilators, such as caffeine, aminophyllin, or theobromine, may be tried without causing further damage. Surgical procedures, in the form of ureteral catheterization, are in order to rule out mechanical blockage of the urine flow, but decapsulation of the kidneys should be used only as a last resort.

I wish to express appreciation to Dr. Jean Bailey, of the Department of Pathology, for her help in the post-mortem examinations, and to Dr. William A. Wolff, Chemist, for the bismuth determinations.

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alone and reports favorable results in a young man treated fourteen years previously so successfully as to be able to assume active duty in the Army.

The following case is one of angioma of the vertebrae.

E. L., a white boy, aged 12½ years, was admitted Oct. 2, 1943, to the neurological service of Bellevue Hospital because of increasing numbness of the legs with weakness and loss of function of eight weeks' duration. Temporary diagnosis of a spinal new growth



Fig. 1.—X-ray of involved vertebrae, Oct. 6, 1943.

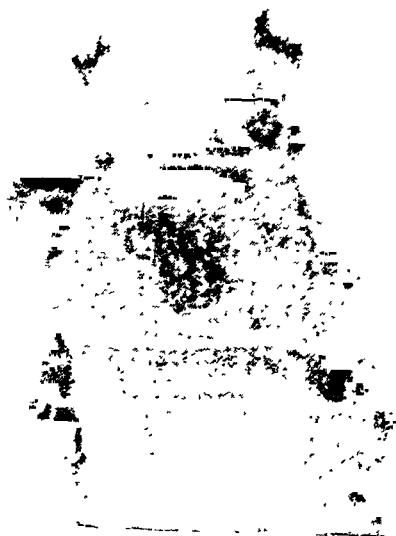


Fig. 2.—X-ray of involved vertebrae after treatment, Feb. 24, 1944.

VERTEBRAL HEMANGIOMA IN CHILDREN

IRA I. KAPLAN, M.D., B.Sc.
NEW YORK, N. Y.

THE usual hemangioma seen in children referred for irradiation is the superficial lesion or birthmark on the skin. Hemangiomas are congenital to quote Ewing¹ "of early development, slow in growth and benign in course." Such as appear on the face are most readily recognized and usually attended to early for cosmetic reasons. The less common hemangioma is that involving bone, whose symptoms resemble various other conditions, and where only the x-ray examination suggests an hemangioma by reason of the characteristic striated effect. The child usually complains of pain in the back and gradually exhibits signs of functional disturbances of the limbs. During the past two decades there were but five cases of bone hemangioma referred for treatment to the Radiation Therapy Department at Bellevue Hospital, and the case reported herein is the only one in a child with vertebral involvement.

Geschickter and Copeland² report that the number of verified cases of bone hemangiomas is small. In most instances their finding is incidental to examination following trauma or in cases involving the spine when neurological symptoms demand attention. The x-ray shows a characteristic soap-bubble effect.

Friedman³ describes as follows the x-ray appearance of hemangioma of bone: "Benign angioma in bone is revealed in the early stages as a circumscribed area of rarefaction; later, the presence of coarse striations and, at times, loculations is also observed. The tumor in flat bones is usually revealed by the characteristic "sunburst" trabeculations radiating from a common center. The lesion in tubular bones may cause cortical destruction but no periosteal perforation, hence the tumor is well circumscribed even beyond the confines of the involved bone."

According to Blackford,⁴ "Hemangiomas of the vertebrae have been noted in more than 10 per cent of a large series of routine autopsies, more commonly in older persons and in females." X-ray reveals coarse, vertical striations and trabeculations which may extend to the pedicles. The vertical diameter of the body of the vertebra and the intervertebral spaces are not disturbed. Symptoms are due not so much to the presence of hemangioma as to the encroachment on the spinal canal, with effects due to compression of the cord. When they occur in young males, Blackford says, they seem to cause symptoms relatively often. He also states that when symptoms suggest tumor of the spinal cord possibility of hemangioma of the vertebrae should be borne in mind.

In cases of hemangioma of the vertebrae, if diagnosis is made before irreparable damage to the cord has taken place irradiation may be expected to effect a cure and Blackford reports cures in twelve cases treated by irradiation

From the Radiation Therapy Department, Bellevue Hospital, New York University College of Medicine.

was made, but the x-ray at this time was suggestive of hemangioma (Fig. 1). On Oct. 9, 1943, a laminectomy was performed at the level of the third to the sixth dorsal vertebrae. A section of tissue was removed for biopsy and the pathology proved the lesion to be a hemangioma. At this time there was complete inability to move the legs and some pain in the spine. He was referred to the Radiation Therapy Department for further treatment and on Oct. 27, 1943, x-ray therapy was started and continued until Nov. 9, 1943. High voltage x-ray filtered through 0.5 copper was administered and 2,000 r was given over the area of the fourth to the eighth dorsal vertebrae. Slight improvement followed. On Jan. 19, 1944, after a second course of x-ray administered from Jan. 6 to 19, 1944, with 2,000 r given, noticeable improve-



FIG. 5.—A picture showing present condition, healed scar, and straight back of the child following operation and treatment.

ment followed. From Feb. 24, to March 13, 1944, another course of x-ray therapy was given, directed at the anterior vertebrae areas through the mediastinum; 600 r was administered. From April 13, to May 31, 1944, x-ray therapy of a dose of 1,500 r was administered. X-ray examination on Feb. 24, 1944 (Fig. 2), still showed the striations in the vertebrae, but the condition of the boy was markedly improved; he was able to stand and walk without difficulty, and there was no interference with skeletal growth. X-ray examination on April 6, 1944, showed no essential change in the appearance of the body of the fifth dorsal vertebrae. The clinical condition, however, gave evidence of regression and healing. The patient was up and about, walking without difficulty and in a happy mental state. There is no evi-



Fig. 4.—X-ray of the spine taken six months after last visit, Sept. 24, 1945.



Fig. 3.—X-ray of involved vertebrae after treatment, March 20, 1945.

The Social Aspects of Medicine

I wrote Professor Lichtenstein several months ago asking him if he would not write an exposition of the Swedish system of medical care, with his criticisms, for the JOURNAL OF PEDIATRICS.

I think that every member of the Academy ought to read it in order that he may become conversant with the system of medical care in another part of the world. I shall try later to obtain expositions of the system of medical care now in operation in England and of the one in New Zealand.

E. A. P.

THE SYSTEM OF MEDICAL CARE OF CHILDREN IN SWEDEN

A. LICHTENSTEIN
STOCKHOLM, SWEDEN

Sweden is one of the smaller countries of Europe as regards population, the number of inhabitants on Jan. 1, 1945, being 6,597,348. In area, however, (449,000 square kilometers) the country is relatively large, somewhat smaller than France and nearly 50 per cent larger than Great Britain and Ireland. The country is, therefore, in parts very sparsely populated. Industrialization has led to an increasingly large influx into the cities. This is shown by the following figures:

CITY INHABITANTS IN PER CENT OF THE WHOLE POPULATION OF SWEDEN							
Year	1840	1860	1880	1900	1920	1940	1945
Per cent	9.67	11.26	15.12	21.49	29.40	37.24	41.49

Sweden is divided into twenty-four counties. The six largest towns do not belong to any county but have their own independent administrations. These towns are: Stockholm, with a population of 654,864; Gothenburg, with 309,348; Malmö, with 167,885; Norrköping with 75,792; Hålsingborg, with 65,375, and Gävle with 40,988. All these figures are for Jan. 1, 1945.

Medical Training.—Medical training is long and thorough, and takes, as a rule, from eight to ten years after matriculation (Studentexamen) which is usually taken between the ages of 18 and 20. Medical training is paid entirely by the state. Apart from certain special courses, medical students do not pay any fees for instruction, which means that even those of limited means can study medicine. Every medical student does a three-month course in pediatrics, which has been an obligatory examination subject for more than one hundred years.

Specialist Training.—Specialist training takes, in most cases, at least three years. Due to an insufficiency of salaried posts, specialist training cannot, as a rule, be started before from two to five years after the qualifying medical (Licentiate) examination. In order to advertise as a pediatrician, three years at least of hospital training at a children's hospital are required, or, as an alternative, at least two years' similar training in addition to a third year which can be devoted entirely to internal medicine or epidemiology, and partly to other fields of medicine important to a pediatrician, such as pulmonary tuberculosis, otology, orthopedics, psychiatry. The number of qualified pediatricians is for the moment only about 120.

The Control of the Health Service and Medical Care.—The control of the health service and medical care is entrusted in Sweden to the Medical and Health Board, organized in dif-

dence of paralysis in any part of the body. (Not always in cases of bone lesions does definite change appear in the x-ray film, though clinical improvement is quite marked. This explains the similarity in the roentgenographs before and after treatment in this case.)

The patient was discharged home and kept under observation. In March, 1945, roentgenograms were again taken of the spine and a moderate resolution of the lesion was noted, there was increased density, probably due to the deposition of calcium from irradiation.

Examination of the boy on April 26, 1945, revealed a good general condition with gain in weight. He walked well without assistance, and had no complaints.

Because of the picture of residual involvement in the affected vertebrae further x-ray therapy was advised and during the period April 26, to June 1, 1945, 1,000 r of high voltage x-ray therapy was administered to the involved dorsal vertebrae area.

On June 11, 1945, he was again examined. His general condition was excellent; there were no complaints, posture was good, and there was no paralysis.

At time of writing (August, 1945) the lad was at home, free of symptoms, happy, lively, and carrying on in the usual manner of boys. There has been no retardation of body growth and he stands erect without difficulty.

Addendum.—The boy was again seen January, 1946, in good health.

SUMMARY

Hemangioma of the bone is not common. It frequently involves the spine. Irradiation is the method of choice. Surgery is recognized in some cases to relieve pressure on the cord. A case is reported showing the favorable results of treatment.

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have him insured as a general rule without a special fee. For such a child, compensation for medical care is given in the case of sickness.

At the end of the calendar year 1943-1944, 2,147,174 persons were members of approved sick relief funds, a figure corresponding to 41.5 per cent of the population of the country over the age of 15 years. At the same time, 763,184 children were insured through the membership of their parents, corresponding to 56.4 per cent of the children of the country under the age of 15.

The sick relief fund movement, of which membership has hitherto been voluntary, has, it is true, spread widely, and the number of members has increased very rapidly. In spite, however, of the relatively low contributions to be paid, a large number of those who are worst off financially are still not members. The Government, after an investigation which has already been carried out, now intends to propose a general obligatory sick relief fund insurance for everyone, a project which seems likely to be enforced in the very near future.

The Senior Medical Officers.—The senior medical officers of hospitals are appointed by the state at the suggestion of the Medical and Health Board. These doctors are either appointed for the entire period until retirement with pension (which in Sweden is 65 years of age) or for a certain period (as a rule from five to ten years), in which case the appointment is usually renewable until the age of retirement is reached. Chief medical officers can, therefore, in practice not be dismissed unless they commit some serious error in the discharge of their official duties, or a breach of the common law.

House Physicians and Assistants.—House physicians and assistants are appointed by the principals of the hospital in question, usually for a period of from one to five years. The appointments can, as a rule, be renewed once, or even several times. Due, however, to the lack of a sufficient number of salaried appointments, there is at present a tendency to try to limit the years of appointment for house physicians and assistants, and at the same time to create assistant Chief Medical Officers posts which can be held for a longer period.

The doctors appointed at the hospitals are paid by the principals of the hospitals. The Chief Medical Officer is responsible for the examination and treatment of the patients admitted to the hospital and also for the reception and treatment of patients in the dispensary. In the latter case, the fees to be paid, partly voluntarily and partly through agreement, have been fixed so low that it is possible for practically any sick person to visit a specialist. The sick relief fund pays a certain part of the doctor's fees for its members. Besides his hospital work, the specialist has the right to private practice and is, in this instance, not bound by any fixed scale of fees.

In the children's hospitals in the larger cities there are, as a rule, outpatient departments where persons of little or no means can receive specialist treatment at a very small fee, usually paid by the sick relief fund. This fee is, as a rule, about 1 to 2 Swedish crowns per visit (from 25 to 50 cents), and no fee is charged if a so-called social certificate of lack of means is produced.

The Care of Outpatients.—The care of outpatients is given in large cities by pediatricians and in the countryside by practicing doctors and provincial public health officers. The two latter groups of doctors have, as a rule, no very extensive pediatric training.

The Pharmacy System.—The pharmacy system in Sweden is based upon personal concession by the Government to a vacant pharmacy. The sale of medicines, especially of poisons, is in general restricted to the pharmacists. The supervision is vested in the Medical Board, which also fixes the prices of medicines by a tariff issued once a year.

Prophylactic Treatment.—Prophylactic treatment begins with prenatal care during pregnancy. This is given partly at maternity centers and partly by private physicians.

Confinements.—Confinements take place in a rapidly increasing degree at maternity hospitals. While in 1930 only 24 per cent of births took place at maternity hospitals, the figure had risen in 1940 to 65 per cent, and in 1943 to 73 per cent.

The care of infants and sick infants at the maternity hospitals has for long been unsatisfactory, on account of unsuitable premises and a lack, both quantitative and qualitative, of suitable personnel for their care.

ferent medical bureaus for hospitals, medical practice, hygiene. The Board is assisted by a scientific council composed of members representing different specialities, medicine, surgery, pediatrics, child welfare.

The Treatment of Inpatients.—The treatment of inpatients is cared for by hospitals, owned and operated by the county councils or, in the case of the above-mentioned six towns by their municipal authorities, with the help of taxation. As a rule, only the university clinics are built by the state, partly in cooperation with the counties or, in Stockholm, with the municipal authorities. The care of the physically sick devolves therefore upon the local authorities. The institutions for the care of the mentally diseased, on the contrary, are mostly built by the state.

It is our aim to have a central hospital with special departments of all kinds in every county. The care of sick children was, however, for a long time neglected by the state and the municipal authorities, and was cared for by private charities. Nowadays, however, children's hospitals and children's wards in the hospitals are built by the counties, with the aid of state contributions both for the actual building and for maintenance, at a rate based on the provision of two hospital beds for children per 10,000 inhabitants. Besides these children's wards in the county hospitals, there are university clinics (two in Stockholm, one in Upsala, and one in Lund), as well as children's hospitals or children's wards in each of the above-named six larger towns. At the present moment, the number of children's hospitals and children's wards in Sweden is twenty-four, with altogether about 1,300 beds. A number of new children's wards are planned and are partly in the process of building.

Care at the county hospitals is intended, in the first place, for those actually resident in the county. At the university clinics and to a certain extent at other children's hospitals, patients are accepted from any part of the country. State contributions to the maintenance make it possible for the costs to the patients to be kept on a very low level. As a rule, the cost per day at a children's hospital is 1.50 Swedish crowns (about 40 cents). These costs, which include x-ray and other special examinations, are paid for entirely by the sick relief funds for their members. The remainder of the actual cost, which amounts to from eight to ten times more than the sum actually paid by the patients, is taken care of by the principals of the hospitals and, in the case of children, with the help of state subsidies.

Sick Relief Funds.—Since 1931, the sick relief funds are regulated by the state. Those contributed to by the state are known as approved sick relief funds, and are under state control. Such a sick relief fund is legally bound to accord to its members certain minimum advantages in the form of sick pay and maternity help. Due to state subsidies, the contributions of members to the funds can be kept very low, which allows even those with very low incomes to become members. The benefits offered by an approved sick relief fund are therefore considerably higher than those corresponding to the contributions paid into the fund.

Sick pay consists partly of compensation for medical care for the direct costs of the sickness (for medical attendance a maximum of two-thirds of the cost, and for hospital treatment the entire costs in a public ward), and partly of sick pay, which constitutes a certain compensation for partial or total loss of earned income due to inability to work during the period of sickness. This is calculated at a fixed sum per day.

Since the compensation for medical attendance is calculated at two-thirds of the cost, according to a fixed so-called "medical care scale," intended only to regulate the financial relations between the insured person and the sick relief fund and not as a binding scale of charges for the doctor, it carries with it the important advantage both for the patient and for the doctor, that the patient can be attended by the doctor of his choice, even if he is a specialist with relatively high fees. In the latter case, however, the insured person must himself contribute a larger sum of money than were he to be attended by a general practitioner.

Maternity aid, which is given to every woman member of the sick relief fund when she is confined, consists of a cash sum of money, at present at least 110 Swedish crowns (as a rule, 125 Swedish crowns).

Entry into the sick relief fund can, as a rule, take place between the ages of 15 and 45. A member who registers his or her healthy child under the age of 15 years can

CONCLUSIONS

Child mortality in Sweden is low and is continually on the decrease. In 1900, infant mortality was 7 to 8 per cent; in 1930, 6 per cent; in 1940, 4 per cent; and in 1944, 3 per cent. The neonatal mortality (death in the first week after birth) has, however, decreased only very slightly, and today constitutes, therefore, a higher percentage of infant mortality than previously. It is hoped, through improved care during confinement, and more efficient care of the newly born child, under the supervision of pediatricians, to decrease the early infant mortality. At the moment, special interest is paid to the care of premature infants. They are taken care of, in an increasingly greater number, at children's hospitals.

As can be seen from this account, we have in Sweden a combined system of state and private medical care. The state and the municipality, partly with the help of the sick relief funds, ensures that every sick person, irrespective of his financial situation, has the opportunity of obtaining the best possible medical care either in the hospitals or outside. To this end, the best specialists in the country in various fields are available as salaried medical officers at hospitals and as doctors for outpatients. The patient has, to a great extent, a free choice of physician. *In my opinion, the free choice of a physician is necessary, for the patient, and for the physician, even in the case of members of sick relief funds, which embrace the largest proportion of the country's population.* The medical profession in Sweden is free, so that the individual doctor can, within a wide boundary, of his own free will choose the place and type of his activities. Even doctors appointed by the state or the municipalities are entitled, in so far as their work at the hospital permits, to carry on their profession with complete freedom.

This system has, in my experience, functioned well, and on the whole fulfills the wishes of both the patient and the doctor. It is my opinion that a substantial state subsidy and control is necessary, if the health and care of the sick in a country are to function effectively and satisfactorily. The fears expressed by some doctors, that a state activity as regards medical care would hamper or prevent the practicing doctor's exercise of his profession, have proved themselves to be unjustified. On the contrary, the work, for example, of the child welfare centers has increased the interest of the public in child welfare and the care of sick children, and private pediatricians are sought in an ever-increasing degree. Such a development, however, presupposes that the state medical activities are not so organized as to make private medical practice impossible. *I fear that should medical activities be entirely controlled by the state, this would, in all certainty, lead to an unfortunate medical bureaucracy and also to an elimination of the personal contact between the patient and the doctor, which is a necessary condition for all good medical activity.* Such a socialization would mean, for the medical profession, a lowering of the standard which is in direct opposition to the interests of the country. *The duty of the state, is, however, to organize medical care in such a manner that every person, irrespective of his income, can procure the best preventive and curative medical care.*

In my opinion, the Swedish system shows very clearly that this can be done without undermining private medical practice.

January 24, 1946

Dr. Edwards A. Park
Johns Hopkins Hospital
Baltimore 5, Maryland

Dear Doctor Park:

I am enclosing a letter which I have written and on which I would like to have your opinion. I have gotten into this discussion rather unwittingly because Dr. White, who is President-Elect of the New York County Medical Society, asked me for my opinion. If you want to use this for your column in the JOURNAL OF PEDIATRICS you are free to do so.

With kind regards, I am,

Sincerely yours,

ALEXANDER T. MARTIN, M.D.

It is only recently that pediatricians have been given the opportunity of working on a large scale at maternity hospitals. At the present moment, in Stockholm, for example, a pediatrician is appointed at every maternity hospital, with the task of supervising the care of the infants and of treating sick infants there.

Sweden has, since 1937, a state organization of maternity and child welfare centers covering the whole country. These are organized as follows: Maternity centers of Type I and child welfare centers of Type I are under the charge of, respectively, a specially trained obstetrician or pediatrician, as a rule the chief medical officer of a department of the hospital, with a full-time nurse to help him. Corresponding centers of Type II are designed for towns and closely populated areas without access to specialists. Type III are known as maternity and child welfare stations and are spread over the whole country. At these stations, the care of the mothers and children is entrusted to the provincial medical health officers, with the aid of the district nurses and district midwives.

In 1944, there were 26 maternity centers of Type I, 77 child welfare centers of Type I, 33 maternity centers of Type II, 31 child welfare centers of Type II, 31 combined maternity and child welfare centers of Type II, and 416 combined maternity and child welfare stations (Type III) with 587 affiliated branches. The sum total of maternity and child welfare centers was, in 1944, 1,193, and the number of surgeries held 45,601.

Care at maternity and child welfare centers is entirely free of charge. Where necessary, prophylactic medicines, cod-liver oil, calcium and similar supplies can be requisitioned free, and are paid for by the state. Only health care can be obtained at the child welfare centers, but at the maternity centers, sicknesses are also treated.

Health control at child welfare centers is entirely voluntary, but attendances must be considered as good. Of 133,167 children born in 1944, 106,899 were under control, a figure which corresponds to 79 per cent. In certain of the larger towns, the percentage under control is even higher. For example, in Gothenburg, the figure is 90 per cent, and in Norrköping, nearly 90 per cent.

This care covers the first year of life. We are endeavouring to place children over the age of one year under the control of the centers. In Stockholm and Gothenburg, all children to the age of entering school already have this possibility. In other parts of the country, children to the ages of 2 to 3 are under control. The organization already described is in the process of rapid development. The lack of a sufficient number of trained pediatricians and insufficient pediatric training for state-appointed public health officers, constitutes a certain difficulty in the growth of the plan. An improvement in this situation is under way.

Health Care of Children of School Age.—Health care of children of school age is entrusted to the school doctor, who is assisted by a school nurse. The system of school doctors, which has for a long time left much to be desired, has now an organization covering the entire country. The aim is to place every child at school under the care of a competent school doctor. Training in pediatrics is, as a rule, a deciding factor in the appointment of a school doctor.

Mental Care in Schools.—Mental care in schools is rapidly increasing. Preventive and medical mental care of children is at present also organized by the State. We aim at having as a leader of this activity a child psychiatrist in each county, assisted by a psychologist and social assistants. This organization however, has only hitherto been practiced on a very small scale.

In the largest cities there are special advisory bureaus to deal with questions of child guidance. Children who have educational difficulties and difficulties of adaptation are also accepted in large numbers at the children's clinics for more thorough investigation.

Care of Handicapped and Others.—The care of the blind, the deaf and dumb, invalids, epileptics, and mentally deficient is taken care of by special organizations. A description of the activities of such organizations would take up too much space here. The costs of such care are borne partly by the state and partly by the municipalities by means of taxation.

I would stress the fact that this comprehensive survey is being made by physicians themselves and could be a model for other professional groups to follow.

The pamphlet *Stepping Stones to Regimentation*, which has provoked this discussion, does a disservice to the profession. We should set our sights higher. If we do not, we will miss the boat.

ALEXANDER T. MARTIN, M.D.
107 East 85th Street
New York City.

Dear Dr. Park:

In recent years a number of bills have been introduced in Congress and in State Legislatures which would authorize the appropriation of considerable sums of money to finance Medical Care Programs. There has been considerable criticism and opposition to these bills on the basis that they would result in a government dominated medical profession, and that this would mean a poor type of medical care.

It is generally accepted that there is a considerable group of the population, perhaps one third, which cannot afford to purchase the medical care which they need. It is also recognized that voluntary insurance plans can hope to provide care only to those individuals in families with sufficient incomes to pay the insurance premium. This leaves the indigent and medically indigent groups still to be provided for.

Most of the criticism of pending medical care bills has failed to offer alternative suggestions which would meet the need. In order to obtain further constructive thinking on these points, will you ask pediatricians to send suggestions to your column as to ways in which public tax funds could be used to bring medical care of high quality to the masses of the population who need it.

Very truly yours,

DEAN ROBERTS

News and Notes

The deaths of the following Fellows have been reported to the JOURNAL:

Dr. G. E. Harrison, Mason City, Iowa

Dr. J. Herbert Young, Boston, Mass.

Dr. Harrison S. Collisi, who retired from the United States Army with the rank of Colonel in December, 1945, has been named medical director of the Planned Parenthood Federation of America, Inc.

The Michael Reese Hospital Post-Graduate School with the cooperation of the members of the Department of Pediatrics, University of Chicago, and Loyola University School of Medicine, will offer a course in Pediatrics. The course will be held at Michael Reese Hospital from May 1 to May 29, 1946; full time; tuition, \$100. Write to Dr. Samuel Soskin, Dean, Michael Reese Hospital Post-Graduate School, Twenty-ninth Street and Ellis Avenue, Chicago 16, Ill.

The Pediatrician and the War

Promotions of the following Fellows have been reported to the JOURNAL:

Captain William T. Ball, Charleston, S. C., to Major

Lieutenant Colonel Lewis Webb Hill, Boston, Mass., to Colonel

Colonel Warren C. Fargo, Cleveland, Ohio, has received the Legion of Merit Medal for his work at Fort Sam Houston.

The following Fellows have been released from the Armed Services:

Dr. Charles E. Anderson, Jr., Shreveport, La.

Dr. George E. Anthony, Flint, Mich.

Dr. Lawrence C. Bachmann, Pittsburgh, Pa.

Dr. William J. Ball, Charleston, S. C.

Dr. Jack Basman, Charleston, W. Va.

Dr. Franklin A. Benes, Shaker Heights, Ohio

Dr. Arthur P. Black, El Paso, Texas

Dr. William W. Briant, Jr., Pittsburgh, Pa.

Dr. Hugh A. Carithers, Jacksonville, Fla.

Dr. Sims A. Chapman, New Orleans, La.

Dr. E. H. Christopherson, San Diego, Calif.

Dr. Enos Paul Cook, San Jose, Calif.

Dr. Robert J. Cooper, Pontiac, Mich.

Dr. Paul C. Crone, Cleveland, Ohio

- Dr. Joseph H. Davis, Palo Alto, Calif.
Dr. Harry F. Dietrich, Beverly Hills, Calif.
Dr. George D. Doroshow, South Gate, Calif.
Dr. R. Cannon Eley, Boston, Mass.
Dr. L. M. Epstein, El Paso, Texas
Dr. Geoffrey W. Esty, Westfield, N. J.
Dr. Merrill W. Everhart, Dallas, Texas
Dr. Herman W. Farber, Petersburg, Va.
Dr. Warren C. Fargo, Cleveland, Ohio
Dr. Clarence Dixon Fowler, Atlanta, Ga.
Dr. Stanley S. Freedman, Providence, R. I.
Dr. Leo S. Friedman, Cincinnati, Ohio
Dr. Harvey F. Garrison, Jr., Jackson, Miss.
Dr. Eugene Gettleman, Sherman Oaks, Calif.
Dr. Ernest L. Glasscock, Kansas City, Mo.
Dr. John K. Glen, Houston, Texas
Dr. Moe Goldstein, Forest Hills, L. I., N. Y.
Dr. Milton M. Greenberg, Washington, D. C.
Dr. Leo Grossman, Miami Beach, Fla.
Dr. Daniel C. Hackett, Rochester, N. Y.
Dr. Salmon R. Halpern, Dallas, Texas
Dr. Albert S. Harden, Jr., Maplewood, N. J.
Dr. Paul Harper, Bridgeport, Conn.
Dr. Joyce I. Hartman, Cleveland, Ohio
Dr. Anna Luvern Hays, Tulsa, Okla.
Dr. George Heller, Englewood, N. J.
Dr. A. Morgan Hill, Grand Rapids, Mich.
Dr. Lewis Webb Hill, Boston, Mass.
Dr. F. Read Hopkins, Lynchburg, Va.
Dr. William A. Howard, Washington, D. C.
Dr. James G. Hughes, Memphis, Tenn.
Dr. Martin J. Hurst, Hollywood, Calif.
Dr. Benjamin M. Kagan, Richmond, Va.
Dr. Joseph M. Klein, Wilkes-Barre, Pa.
Dr. George S. Littell, Plainview, Texas
Dr. Russell W. Mapes, Beverly Hills, Calif.
Dr. Herman B. Marks, Pawtucket, R. I.
Dr. John Walker Maroney, Wilmington, Del.
Dr. R. J. Martoccio, Utica, N. Y.
Dr. R. A. McGuigan, Evanston, Ill.
Dr. John C. McKittrick, Burlington, Iowa
Dr. Henry S. Meyer, Houston, Texas
Dr. John Fleek Miller, Newark, Ohio
Dr. Stephen Dow Mills, Westfield, N. J.
Dr. John McKenney Mitchell, Rosemont, Pa.
Dr. H. J. Morrison, Savannah, Ga.
Dr. Paul N. Morrow, Omaha, Neb.
Dr. Samuel J. Nichamin, Detroit, Mich.
Dr. Ernest L. Noone, Drexel Hill, Pa.
Dr. Edward T. O'Donnell, Wilmington, Del.
Dr. Owen S. Ogden, Louisville, Ky.
Dr. Alfred W. Pinkerton, Lima, Ohio
Dr. Harold D. Pyle, South Bend, Ind.
Dr. William A. Reilly, San Francisco, Calif.
Dr. Harold E. Roe, Pomona, Calif.

- Dr. H. A. Rosenberg, Waterbury, Conn.
Dr. Herman Schneck, New York, N. Y.
Dr. Joseph Schwartzman, Brooklyn, N. Y.
Dr. Charles Lee Shafer, Mansfield, Ohio
Dr. John J. Shields, 7500 Brookfield Road, Philadelphia, Pa.
Dr. H. Herman Shuman, Springfield, Mass.
Dr. Carl E. Sibilsky, Peoria, Ill.
Dr. Henry Siegel, Detroit, Mich.
Dr. Walter J. Siemsen, Kalamazoo, Mich.
Dr. Irving Silverman, Roxbury, Mass.
Dr. Lendon Snedeker, Boston, Mass.
Dr. George E. Stafford, Lincoln, Neb.
Dr. Albert F. Stein, Chicago, Ill.
Dr. Neil C. Stone, Poughkeepsie, N. Y.
Dr. Vincent G. Tosti, Ridgewood, Queens, N. Y.
Dr. Alfred A. Trivilino, Jamaica, N. Y.
Dr. James H. Wallace, Oak Park, Ill.
Dr. Charles E. Ward, Jackson, Miss.
Dr. Thomas S. Weaver, Nashville, Tenn.
Dr. George H. Wegmann, Milwaukee, Wis.
Dr. Robert L. Wilder, Minneapolis, Minn.
Dr. R. E. Williams, Chicago, Ill.
Dr. Sherl J. Winter, Dayton, Ohio
Dr. Irving J. Wolman, Philadelphia, Pa.
Dr. J. Andreas Wunderlich, Jr., Pittsburgh, Pa.

Book Reviews

Your Child From One to Six. Children's Bureau Publication 30, U. S. Department of Labor, Washington, D. C., 1945, 146 pages. (May be obtained from the Superintendent of Documents, U. S. Government Printing Office, Washington, D. C.) Price 15 cents.

This 1945 revision of *Child Care—The Preschool Age*, which was first published in 1918 and has had several earlier revisions, is the soundest and safest book in print to place in the hands of the average mother with a young child. It has been carefully written and the text reviewed by a number of outstanding pediatricians, child psychologists, and psychiatrists. The text is closely in keeping with modern thought and is free from the didactic rigidity which marred the earlier editions. The authors in a remarkable way have put technical thought and procedures into good simple English which does not need a glossary or dictionary to be understood. It should and will have a tremendous circulation as every doctor can recommend it to the parents of young children. The authors and Children's Bureau are to be congratulated on having produced such an excellent book on child care and training.

B. S. V.

Men Without Guns. The Story of Army Medicine. Text by DeWitt Mackenzie. Illustrated with 137 plates (118 in color), from the Abbott Collection by Contemporary Artists, Philadelphia, 1945, The Blakiston Company. Price \$5.00.

Not only the medical profession, but also the people of the United States are indebted to the Abbott Laboratories for making possible this remarkable graphic presentation of the work of the Medical Corps of the Army in World War II. The idea originated with Lieutenant Colonel Howard Baer, M. A. C., who worked with another Howard Baer, the artist, and Reeves Lowenthal of the Associated Artists, who has done so much to make art available to the rank and file of America. This group interested the Abbott Laboratories in sponsoring the project. With the approval of Surgeon General Kirk, who writes a foreword for the book, a group of outstanding contemporary artists were selected and sent to all the corners of the earth to sketch and paint the work of the Medical Corps.

Many have seen selections from the paintings which have been exhibited in Art Museums in a number of cities and many doctors have carefully put aside in their portfolios the reproductions which have been appearing in recent months in the monthly bulletin of the Abbott Laboratories. Now a selection has been brought together in the volume with an excellent text by DeWitt Mackenzie, war analyst of the Associated Press. While many of the sketches, as would be expected from the nature of the project, are "journalese" in character, not a few in their composition, feeling, and execution rank as works of art which make them stand by themselves. Among them might be mentioned "Anopheles Home Front" and "Night Duty" by Franklin Boggs; "Just Off the Line" and "Men With God" by Robert Benny; "Return Cargo" and "Fireside Comfort" by Lawrence Beal Smith; "Pack Train in China" and the jungle pictures by Howard Baer; "Night Shift" and "Italian Rush Hour" by Joseph Hirsch. The format of the book and printing are excellent, but the color reproductions for some reason or another are not as good as the reproductions in the Abbott Laboratories bulletins.

The collection is now the property of the United States Government. Certainly this vivid portrait of the work of the Medical Corps is a thing which every doctor can look to with pride. A young veteran of New Guinea, Leyte, and Okinawa who returned from Japan a few days before Christmas summed it up. He picked up the book from my desk and quietly looked at the pictures. All he said as he closed it was, "God, those medical guys did a swell job."

B. S. V.

Journal of the History of Medicine and Applied Science. Published quarterly by Henry Schuman. New York.

The appearance of a new journal in medical literature is always a matter of interest, and worthy of examination and note. When a new journal in the history of medicine is issued, special recognition must be given. Such is the case with this new Journal which made its appearance in January, 1946. It is edited by Dr. George Rosen with an able and representative group serving on the editorial board and as consulting editors, the latter group including representatives of many foreign countries and many persons in this country whose names are familiar in the field of the history of medicine.

As stated in the introductory article by the Editor, there is only one other publication in this field in this country, the *Bulletin of the History of Medicine*. The new Journal will supplement the *Bulletin* and provide another focus for studies in medical history. Contributions on all aspects of the history of medicine, public health, dentistry, nursing, pharmacy, veterinary medicine, and the various sciences that impinge on medicine will be published. Papers dealing with limited and specific subjects will be supplemented by occasional articles of wider scope that summarize certain important fields and outline the broad trends in them. Several review articles by competent investigators are contemplated.

The first number contains ten original articles of a wide range of interest. There is also a section entitled *Notes and Queries*, and an abundant section on *Book Reviews* including those of historical interest.

The publisher is Mr. Henry Schuman of New York, long known to students of medical history and to collectors of medical publications of historical interest. His own personal interest in this field will insure proper guidance for the Journal. It is unusual to find a publisher and an editorial staff with such close common interest. A small amount of appropriate advertising appears in the back section.

The form of the first issue as an example of the Journal is satisfying. Laid paper is used which carries printing and illustrations to good advantage. Half-tone cuts are used for inserts. The over-all appearance and effect are pleasing. The printing is done by a well-known firm recognized for high quality of printing standards.

The Editor states several reasons for the decision to issue another publication in medical history. It may be added that during these times when everybody feels that great progress is being made in civilization and in education, science and allied fields, it is helpful occasionally to pause to consider how much is real progress and how much is only change and rearrangement of ideas and feelings. When one pauses, so to speak, to catch breath and look around, it is necessary always to look backward. It has long been recognized that history moves in cycles. New facts are constantly added, but human thinking and utilization of those facts may not always be a forward movement. It is fortunate then, that such publications as this Journal help to bring the hindsight to our perspective and to make the past part of the prologue.

H. M.

In the Doctor's Office. Esther Jane Parsons, Philadelphia, 1945, J. B. Lippincott Company, 295 pages. Price \$2.00.

This is a small book packed full of sound principles and philosophy, useful facts and information, advice and caution and satisfaction. It is good reading for the doctor to see where his responsibilities and difficulties lie and probably what he can do to make the machinery run more smoothly and efficiently in his office. He will surely profit by reading the contents carefully. There is always a new viewpoint or new ideas in such books, and this one is full of such. It is unusually easy to read.

H. M.

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Original Communications

THE RETENTION OF ELECTROLYTE DURING RECOVERY FROM SEVERE DEHYDRATION DUE TO DIARRHEA

DANIEL C. DARROW, M.D.

NEW HAVEN, CONN.

PREVIOUS studies of the changes in the composition of the body produced by diarrhea have considered the evidences of loss of intracellular water and electrolyte as a result of a breakdown of the tissues which is not readily reversible. This interpretation was largely a consequence of the prevailing concepts of the structure of intracellular and extracellular fluids in which the peculiar distribution of electrolyte was considered to depend largely on the exclusion of sodium and chloride from the cells and on the relative impermeability of cellular membranes to potassium. In the past ten years these views have been disproved. It is now clear that intracellular fluids contain appreciable amounts of sodium and chloride, and that potassium readily crosses the cellular membranes. Normally the muscles contain a small amount of intracellular sodium which has been shown to be transferred to the extracellular fluids in one type of acidosis.^{1, 2} Under certain circumstances considerable amounts of potassium are lost from the intracellular phase of muscle and are replaced by almost equivalent amounts of sodium. This change has been shown to occur as a consequence of diets low in potassium,³⁻⁶ after injections of desoxycorticosterone acetate,^{4, 7} in response to certain steroids,⁸ and following prolonged therapy with solutions containing only glucose and sodium chloride.^{9, 10} Certain patients with Cushing's syndrome and refractory alkalosis have a deficit of potassium in their muscles.^{11, 12} Elsewhere the author¹³ has outlined a new framework for the presentation of the disturbances of body water and electrolyte and has developed the concepts which take into account these facts. The present work fits the losses of electrolyte produced by diarrhea into this framework.

From the Departments of Pediatrics of Yale and Johns Hopkins Universities.
This research was aided in part by a grant from the Fluid Research Fund of Yale University.

The author is indebted to many people who cannot be enumerated, but wishes publicly to thank Drs. Edward A. Rabe, Clifton D. Govan, Laslo Kajdi, and Edwards A. Park, Miss Frances E. Coville, Mr. John F. Iannucci, and Mrs. Davis T. Radcliff. Drs. Rabe and Govan assisted in supervising the collections of specimens in New Haven and Baltimore, respectively. Dr. Park provided the facilities of the Harriet Lane Home and the laboratories of the Pediatric Department of the Johns Hopkins University for the work on the last four cases. Dr. Kajdi, in addition to providing a trained personnel from his laboratory, did much to facilitate the work. Miss Coville, Mr. Iannucci, and Mrs. Radcliff assisted in the chemical analyses. The numerous nurses who did the difficult task of collection of specimens must be thanked as a group. The success of this phase of the work reflects the high state of morale of the nursing schools at Yale and Johns Hopkins and is a measure of the effectiveness of the teachers of these schools.

The general plan of the experiments was to obtain the actual retentions of the chief extracellular and intracellular ions during recovery from the dehydration of severe diarrhea. The patients were considered to have recovered when they were taking adequate food and gaining weight for two or more days. In the six cases which will be reported, this criterion was met in all but Cases 3 and 4 and these patients were gaining two days after termination of the study. It was hoped that the gain in weight on normal intake would indicate normal tissue water and electrolyte, and hence that the retentions would equal the deficits at the beginning of the study. It was not expected that tissues consumed as a whole with loss of nitrogen, phosphorus, and potassium would be reconstituted, but it was anticipated that those present in the body would have an essentially normal composition with respect to nitrogen, phosphorus, and potassium; that is, the body would be normal except for the results of starvation. Analyses of the muscles of cats subjected to nine days of starvation do not show any change in the composition of muscle per unit of fat-free solids. As will be pointed out later, the retentions of sodium and chloride are so large that some of the gain in weight must be considered due to overexpansion of the extracellular fluids. Within the cells, the retentions of potassium and phosphorus almost certainly represent true deficits on admission, since excessive retentions of these ions are unlikely and, in experimental animals, have been produced with respect to potassium only by raising the extracellular concentrations to abnormally high levels. However, the experiments provide no criterion by which to judge whether longer periods of observation would have led to even greater retentions before nitrogen, phosphorus, and potassium could be retained in the normal relations to each other.

During the balance studies, the usual therapeutic measures were carried out. In the first four cases, no potassium was given parenterally during the period of fasting, while potassium was given parenterally in the last two cases. The studies, therefore, permit a comparison of the effects of the conventional therapy with the new type which uses potassium salts, parenterally and from the beginning of the therapy directed toward replacement of water and electrolyte.

METHODS

Immediately on selection of the case, blood was taken under mineral oil and the baby placed on a metabolism bed so as to collect urine and feces separately. Urine was preserved with thymol or toluol and collected over the period of time without catheterization. Stool collections were started immediately and the end of each period demarcated by giving a small amount of carmine by mouth. At the end of each period a sample of blood was taken. During the first period nothing was given by mouth, and fluid intake and replacement therapy was instituted by giving a slow intravenous drip of solutions containing sodium chloride, sodium lactate, and glucose in the first four cases and by giving potassium chloride, in addition, in the last two cases. Blood and plasma were also given when indicated on clinical grounds. The exact intakes are given in the tables and the case protocols. During the second period food at submaintenance levels of intake was given, while in the third period maintenance

feeding was given except in Case 4. As noted in the protocols, parenteral fluid was given in Period II of Case 4. Potassium chloride was added to the food during Period II in all but Case 6. The basic food in all cases was a mixture of powdered whole milk and powdered skimmed milk, in order that the mixture have about 2 per cent fat and 3.5 per cent protein. Dextrimaltose equal to 10 per cent of this mixture was added. In Case 3 the dextrimaltose contained sodium chloride, but in the other cases it was free of salt. The food mixture was usually diluted with sufficient water to give adequate fluid intake. The exact intakes are shown in the tables and protocols.

All food, intravenous solutions containing electrolyte, and excreta were analyzed in duplicate on separate aliquots. The intakes of intravenous fluids containing electrolyte were measured by weighing the bottles; glucose solutions were measured by volume. In the last two cases the intakes by mouth were measured by weighing the bottles, but in the first four cases the measurements were by volume. When transfusions were given, only the electrolyte content of the plasma was considered in the balances.

The chemical methods were those in previous use by the author.¹ A glass electrode at 38° C. was used to measure the pH in the first two cases. Unusual values — particularly serum chloride and sodium — were rechecked. A Waring mixer was used for the stools, and aliquots obtained by weighing a well-mixed portion. In all analyses the checks were better than 2 per cent. Excepting the loss of about 50 Gm. of stool in Period II of Case 6, no serious error in the collections is known to have occurred. There was no vomiting in any case and in all but Period II of Case 4, little food was refused.

CALCULATIONS

The tables present the serum concentrations and the balances in the usual manner. The charts show the cumulative balances at the end of each period in intracellular and extracellular fluids. In order to make the different cases comparable, the cumulative balances in the charts were adjusted to balances per 10 kg., using the final body weight in making this calculation. The figures to the right of the charts are estimated normal contents of a 10 kg. child.¹³

The calculations used in constructing the charts have been previously described and applied.^{2, 14} In calculating the distribution of the balances, the following assumptions were made: (1) that the concentration of sodium and chloride in extracellular water is measured by that of an ultrafiltrate of serum,* (2) that the initial volume of extracellular water is 20 per cent of the weight on admission, (3) that the balance of chloride represents a change in extracellular chloride only.

Using brackets [] to indicate concentrations and parentheses () to indicate amounts, the following equations are self-explanatory.

$$\begin{aligned} & \text{(Initial extracellular H}_2\text{O)} [\text{Initial extracellular Cl}] = \text{(Initial extracellular Cl)} \\ & \text{(Initial extracellular Cl)} + \text{(Balance Cl)} = \text{(Final extracellular Cl)} \\ & \text{(Final extracellular Cl)} \div [\text{Final extracellular Na}] = \text{(Final extracellular H}_2\text{O)} \\ & \text{(Initial extracellular H}_2\text{O)} [\text{Initial extracellular Na}] = \text{(Initial extracellular Na)} \end{aligned}$$

*The concentration in the ultrafiltrate was derived from the serum concentration of water and electrolyte and an average Donnan factor of 0.96.

$$\begin{aligned} &(\text{Final extracellular H}_2\text{O}) [\text{Final extracellular Na}] = (\text{Final extracellular Na}) \\ &(\text{Final extracellular Na}) - (\text{Initial extracellular Na}) + (\text{Balance Na}) = \\ &(\text{Balance intracellular Na}) \end{aligned}$$

The amount of water is expressed in kilograms; the amount of electrolyte in millimoles and the concentrations in millimoles per kilogram of water. Similar equations were set up for potassium, but no correction for extracellular phosphorus was made owing to the lack of determination of the concentrations of serum phosphorus.

Applying these equations gives the shifts of sodium, potassium, and phosphorus into the cells. However, it does not measure the deviations from normal in the composition of the cells. In order to correct for changes in the amount of cytoplasm it was assumed that when cytoplasm is broken down or reconstituted, the balances of nitrogen, phosphorus, and potassium have the same relation to each other as found in muscle. In the case of phosphorus it was assumed that any balance of calcium would be reflected by a change in bone phosphorus which is indicated by the ratio of Ca:P in bone salts. The following equations express these relationships:

$$\begin{aligned} P &= 2 N + 0.57 \text{ Ca} \quad \text{predicted balance of phosphorus from the balance of N and Ca} \\ K &= 3 N \quad \text{predicted balance of potassium from the balance of nitrogen} \end{aligned}$$

Nitrogen balance is expressed in grams; phosphorus and potassium are expressed in millimoles. Urinary calcium was assumed to be negligible in the last five cases since urinary calcium was so low in Case 1.

RESULTS

Tables I to VI give the balances for each period together with the body weight and the time intervals. Table VII gives the serum analyses. The case numbers and dates indicate which analyses were taken at the beginning and the end of each period. The charts (1 to 6) represent the derived data showing the apparent balances in intracellular and extracellular fluids at the end of each period per 10 kg. of body weight. Since the intracellular balances of these charts are corrected for changes in body nitrogen and calcium, they represent deviations from the balances which would be obtained in a normal baby maintaining a normal composition; that is, a positive intracellular balance may be interpreted as due to a deficit in the cells on admission and a negative intracellular balance indicates a presumptive excess on admission. Note that the charts are constructed on a cumulative basis so that the changes in composition represent changes from the composition on admission.

The following protocols show the relevant facts of the histories. All patients were normal at birth and artificially fed on accepted milk mixtures. Stool cultures were made on all patients but only significant findings are reported.

CASE 1.—The patient was a boy, aged 4 weeks, who had been in the care of an orphan asylum. He had been ill for three days starting with transient cyanotic spells, followed by fever on the second day, and many small, loose stools on the third day. He received a hypodermoclysis of 120 c.c. of artificial interstitial salt solution eighteen hours before admission. On admission he was moderately dehydrated but did not have Kussmaul breathing. The baby passed essentially normal stools in the hospital and recovery was rapid and apparently complete at the end of the study.

Period I lasted for 39.5 hours, from 6:30 P.M. on January 18, until 10:00 A.M. on January 20. Nothing was given by mouth. During this period he received 300 c.c. of a mixture of 180 c.c. of isotonic sodium lactate and 150 c.c. of artificial interstitial salt solution; 77 c.c. of blood; and 1,226 c.c. of a mixture of $\frac{1}{4}$ physiological saline and $\frac{2}{3}$ 10 per cent glucose. His weight changed from 3,500 to 4,060 Gm.

Period II lasted for 49.5 hours, from 10 A.M. January 20, until 11:30 A.M. January 22. On the first day he received 180 c.c. of the milk mixture with 1 Gm. of potassium chloride, and on the second day the same food diluted with 180 c.c. of water. During this period his weight remained 4,060 Gm.

Period III lasted for 72 hours, from 11:30 A.M. January 22, until 11:30 A.M. January 25. During this period the baby took 1,260 c.c. of the milk mixture. The weight changed from 4,060 to 4,300 Gm.

TABLE I. BALANCE IN CASE 1

SOLIDS									BODY WEIGHT
	Gm.	H ₂ O Gm.	N Gm.	Cl mM	Na mM	K mM	P mM	Ca mM	Kg.
Period I (39.5 Hours)									
Intake	108	1,526	0.0	83.0	119.0	0.4	0.0	0.0	3.50
Urine		700	2.06	69.6	51.5	7.65	4.5	0.0	
Stools	3.3	12	0.34	0.3	0.5	1.18	0.6	1.4	
Balance			-2.40	13.1	67.0	-8.43	-5.1	-1.4	4.06
Period II (49.5 Hours)									
Intake	64	476	1.84	35.0	7.9	40.6	9.9	10.3	
Urine		186	0.81	24.1	59.2	16.2	5.7	0.0	
Stools	6	20	0.48	0.0	0.1	1.3	4.2	7.7	
Balance			0.55	10.9	-51.4	23.1	0.0	2.6	4.06
Period III (72 Hours)									
Intake	227	1,033	6.45	45.4	27.1	49.5	34.5	36.0	
Urine		510	2.28	23.7	10.8	31.1	9.8	0.0	
Stools	15	55	0.78	0.3	0.3	3.5	15.9	34.0	
Balance			3.39	21.4	16.0	13.9	8.8	2.0	4.30

CASE 2.—The patient was a boy, aged 2 months. Owing to whooping cough at home, the boy was cared for in a foster home. Here he received somewhat too much food (160 calories per kilogram) and vomited once or twice daily. Two days before the study, diarrhea as well as vomiting occurred. The diarrhea became worse on skimmed milk and barley flour. The second day he had fever and became sicker. On admission he was vigorous but quite sick and dehydrated. The skin turgor was poor and the eyes sunken. The lips were cyanotic, but there was no Kussmanl breathing. Under treatment the stools remained watery for two days and loose for three days. The stools were yellow and pasty after five days. The baby looked well at the end of the study but did not gain regularly until one week after the end of the balance study.

Period I lasted for 50 hours, from 12:00 noon, April 18, until 2:00 P.M. on April 20. He was given nothing by mouth. Subcutaneous and intravenous fluids were given, containing blood, sodium chloride, sodium bicarbonate, and glucose. The weight changed from 3,850 to 4,390 Gm.

Period II lasted for 3 days, from 2:00 P.M. on April 20, until 2:00 P.M. on April 23. On the first day he received a hypodermoclysis of $\frac{2}{3}$ physiological saline and $\frac{1}{3}$ 5 per cent glucose (300 c.c.). For the first two days he drank 720 c.c. of 5 per cent glucose with 3 Gm. potassium chloride. On the last day he drank 148 c.c. of the milk mixture plus 1.5 Gm. potassium chloride, and 270 c.c. of water. The weight remained 4,300 Gm.

Period III lasted for 4 days, from 2:00 P.M. April 23, until 2:00 P.M. April 27. On each day the total food intake measured 600 c.c., and contained 1.5 Gm. of added potassium chloride; on the first day, 300 c.c. of the milk mixture were given; and on the last three days, 450 c.c. The baby looked well, but pale, at the end of the study. The weight changed from 4,300 to 4,380 Gm.

TABLE II. BALANCE IN CASE 2

SOLIDS								BODY WEIGHT
Gm.	H ₂ O Gm.	N Gm.	Cl mM	Na mM	K mM	P mM	Ca mM	Kg.
<i>Period I (2 Days 2 Hours)</i>								
Intake	22	1,113	0.0	80.3	120.8	1.8	0.0	3.85
Urine		160	1.66	9.7	3.3	4.9	9.1	
Stools	8	242	0.61	15.5	15.6	9.7	1.9	1.8
Balance			-2.27	55.1	101.8	-12.8	-11.0	-1.8
<i>Period II (5 Days)</i>								
Intake	44	1,438	0.92	88.4	25.9	68.9	5.4	5.6
Urine		685	0.91	91.3	40.0	26.5	3.6	
Stools	6	188	0.47	16.8	15.5	8.3	1.4	1.6
Balance			-0.46	-19.7	-29.6	34.1	0.4	4.0
<i>Period III (4 Days)</i>								
Intake	304	2,336	8.35	129.8	37.6	151.0	50.4	52.0
Urine		1,455	3.26	133.0	48.3	115.8	22.1	
Stools	28	220	1.66	23.1	1.3	11.5	14.8	49.0
Balance			3.43	-26.3	-12.0	23.7	13.5	3.0

CASE 3.—The patient was a Negro boy born of a tuberculous mother. The baby was taken care of by an aunt and did not have a positive tuberculin reaction. At the age of 4½ months he was treated in the hospital for ten days for diarrhea and dehydration. Four days before the study, at the age of 7½ months, he had several watery stools. The diarrhea continued at this rate until admission to the hospital. Two days before admission, fever developed and the baby became dull and listless. On admission he was quite sick and dehydrated, with poor skin turgor and sunken eyes. There was no Kussmaul breathing. Although he was not extremely sick, recovery was somewhat slow and the stools were still loose at the end of the study. He gained weight two days later and was discharged well after eleven days of treatment, having gained 800 Gm.

Period I lasted for 38 hours, from 10:00 P.M. on August 20, until 10:00 A.M. on August 22. Nothing was offered by mouth and an intravenous drip gave solutions containing sodium chloride, sodium lactate, and glucose as indicated in the table. The weight changed from 6,050 to 6,100 Gm.

Period II lasted 3 days, from 10:00 A.M. on August 22, until 10:00 A.M. on August 25. To each day's food 1.5 Gm. of potassium chloride were added. On the first day he received 55 calories per kilogram and on the last two days 110 calories per kilogram. The weight changed from 6,100 to 6,350 Gm.

TABLE III. BALANCE IN CASE 3

SOLIDS								BODY WEIGHT
Gm.	H ₂ O Gm.	N Gm.	Cl mM	Na mM	K mM	P mM	Ca mM	Kg.
<i>Period I (58 Hours)</i>								
Intake	59	1,492	0.0	88	132	0.0	0.0	6.05
Urine		590	1.77	44	44	6.3	7.9	
Stools	19	156	0.73	3	5	12.0	7.5	14.9
Balance			-2.50	41	83	-18.3	-15.4	-14.9
<i>Period II (72 Hours)</i>								
Intake	380	1,909	11.62	143	105	140.0	81.0	57.9
Urine		672	3.59	79	135	28.7	22.3	
Stools	53	747	0.63	4	17	41.7	15.5	31.5
Balance			7.40	60	-47	69.6	43.2	26.4

CASE 4.—The patient was a boy, aged 10½ months. Four days before admission he became irritable and had several loose stools. The next three days he vomited most of his food and had six to eight stools each day. No blood or mucus was noticed in the stools. The day before admission, his temperature was 38° C. and he received sulfadiazine. On ad-

mission he was well developed and nourished, but quite sick and dehydrated. He was greatly prostrated, and out of contact with his environment though he responded to painful stimuli. The skin turgor was poor; the eyes and fontanel sunken. There was questionable otitis media. The eardrums were not incised and did not discharge spontaneously. Under treatment he improved rapidly but remained irrational for two days. The temperature varied between 37 and 39.5° C. during the first five days. He was still apathetic and had loose stools at the end of the study. He improved markedly and gained weight three days after the study. Although pathogenic organisms were not cultured from the stools, the clinical course suggested bacillary dysentery.

Period I lasted for 2 days, from noon on August 21, until noon on August 23. Nothing was given by mouth. By an intravenous drip, he received fluids containing sodium chloride, sodium lactate, glucose, and 200 c.c. of blood. The stools were watery during this period. The weight changed from 3,149 to 1,198 Gm.

Period II lasted for 4 days, from noon on August 23, until noon on August 27. On the first, second, and fourth days he received an intravenous injection of a mixture of 2% physiological saline and 1/2 sixth molar sodium lactate. In addition he was given 2 Gm. of potassium chloride in 240 c.c. of 5 per cent glucose by mouth. On the third day, feedings of a milk mixture containing added potassium chloride were taken poorly and discontinued. He received 100 c.c. of blood on this day. Improvement was slow but steady during this period. The weight changed from 11.98 to 12.70 kg.

Period III lasted for three days, from noon on August 27, until noon on August 30. On each day 1.5 Gm. of potassium chloride were added to the milk mixture. On the first two days he received about 20 calories per kilogram and on the last day 40 calories per kilogram. Although the stools remained loose, recovery was satisfactory. He was gaining on adequate calories two days after the study was finished. The weight changed from 12.70 to 11.85 kg.

TABLE IV. BALANCE IN CASE 4

SOLIDS									BODY WEIGHT
	Gm.	H ₂ O Gm.	N Gm.	Cl mM	Na mM	K mM	P mM	Ca mM	Kg.
Period I (2 Days)									
Intake	36	1,495	0.0	104	147	0.0	0.0	0.0	11.49
Urine		230	3.35	4	21	6.5	10.6		
Stools	24	538	1.92	25	41	20.2	8.3	6.2	
Balance			-5.27	75	85	-26.7	-18.9	-6.2	11.98
Period II (4 Days)									
Intake	177	2,540	3.48	258	263	98.0	20.0	20.3	
Urine		670	1.90	144	118	33.2	11.4		
Stools	18	405	1.15	23	37	15.5	7.5	7.5	
Balance			0.43	91	108	49.3	1.1	12.8	12.70
Period III (3 Days)									
Intake	230	1,699	5.55	99	60	88.2	35.5	34.6	
Urine		430	2.29	101	44	47.8	10.3		
Stools	25	495	1.43	9	20	19.0	11.3	13.5	
Balance			1.83	-11	-4	21.4	13.9	21.1	11.85

CASE 5.—The patient was a boy, aged 3 months. Seven days before admission he started to have watery stools as often as ten times a day. He vomited frequently from the day of onset. The stools were somewhat less frequent during the last four days, but the baby became listless, looked sicker, and his eyes became sunken. On admission he had a temperature of 40° C. and was extremely sick with marked dehydration, diminished skin turgor, sunken eyes and fontanel, and typical Kussmaul breathing. The skin had the typical grayish pallor of shock. *Proteus morganii* was cultured from the stools. In the hospital his temperature rose to as high as 39 or 40° C. for three days, at which time he looked desperately sick and recovery seemed unlikely. He was discharged well after twenty-three days in the hospital, having gained 800 Gm.

Period I lasted for 97 hours, from 11:00 A.M. on September 4, until noon on September 8. Nothing was given by mouth. By an intravenous drip the following was given: First day, 262 Gm. of a mixture of $\frac{2}{3}$ physiological saline and $\frac{1}{3}$ isotonic sodium lactate; 519 Gm. of a mixture* of potassium chloride, sodium chloride, and sodium lactate; blood, 50 c.c.; plasma, 50 c.c. Second and third days, potassium chloride 2 Gm., and sodium chloride 3 Gm. in 300 c.c. of water; 450 Gm. of 5 per cent glucose and 261 Gm. of a mixture of $\frac{2}{3}$ physiological saline and $\frac{1}{3}$ isotonic sodium lactate. Fourth day, potassium chloride 2 Gm., sodium chloride 3 Gm. in 250 c.c. of water, and 180 c.c. of 5 per cent glucose. During this period the stools weighed 195, 282, and 279 grams on first, second, and combined third and fourth days, respectively. The weight changed from 4,860 to 5,200 Gm.

Period II lasted for 5 days, from noon on September 8, until noon on September 13. On the first day he received intravenously 570 c.c. of 5 per cent glucose containing 2 Gm. potassium chloride and 3 Gm. sodium chloride; by mouth he received 270 c.c. of 5 per cent glucose. On the last three days he received a milk mixture made up to 780 c.c. containing about 20 calories per kilogram. To each day's milk, 1.5 Gm. of potassium chloride were added. The weight remained 5,200 Gm.

Period III lasted for 4 days from noon on September 13, until noon on September 17. He was given a milk mixture made up to 720 c.c. which contained for the first two days about 50 calories per kilogram and on the last two days about 90 calories per kilogram. Improvement was steady and the baby was practically recovered at the end of the study. The weight changed from 5,200 to 5,450 Gm.

TABLE V. BALANCE IN CASE 5

SOLIDS									BODY WEIGHT
	Gm.	H ₂ O Gm.	N Gm.	Cl mM	Na mM	K mM	P mM	Ca mM	Kg.
<i>Period I (4 Days 1 Hour)</i>									
Intake	53	2,292	0.0	282	279	75.1	0.0	0.0	4.86
Urine		508	3.04	115	84	34.4	11.8		
Stools	19	736	1.42	82	89	25.5	4.1	2.6	
Balance			-4.46	85	106	15.2	-15.9	-2.6	5.20
<i>Period II (5 Days)</i>									
Intake	229	3,945	3.52	218	159	149.8	23.3	25.7	
Urine		1,656	2.72	126	56	73.2	13.3		
Stools	33	1,036	1.94	83	66	44.0	9.4	17.1	
Balance			-1.17	9	37	32.6	0.6	8.6	5.20
<i>Period III (4 Days)</i>									
Intake	466	2,497	10.01	67	44	92.5	61.1	62.3	
Urine		1,175	2.41	37	12	39.0	23.3		
Stools	44	494	2.01	23	25	22.9	11.0	40.8	
Balance			5.59	-7	7	30.6	26.8	21.5	5.45

CASE 6.—The patient was a boy, aged 11 months. Two weeks before the patient became sick, a sister, aged 3 years, had diarrhea and fever. Four days before admission, the baby had twelve loose stools which were at first yellow and later green. He was given castor oil on this day. The next day he had six watery stools and vomited all food, though he retained a mixture of sugar and water. The vomiting and diarrhea continued until admission. On the third and fourth days, fever was noted, together with increasing weakness and sunken eyes. On admission he was well developed and nourished, but extremely sick. The eyes were sunken and showed a glassy stare. The skin turgor was very poor and the skin had the typical grayish pallor of shock. The stools were not examined microscopically or by guaiac test but contained no gross blood. For the first five days they were practically clear water, with a few flecks of yellowish material that looked like a desquamated membrane. The stools contained an organism belonging culturally to the Flexner group, but the organism was not agglutinated by Flexner serum. The baby had a fever varying from 38 to 40° C. for two

*The mixture of sodium chloride, potassium chloride, and sodium lactate is described in the discussion.

days and looked so sick for three days that recovery seemed unlikely. He had practically recovered at the end of the study, and was discharged after fifteen days in the hospital.

Period I lasted for 3.7 days, from midnight on September 14, until 3:00 p.m. on September 18. By intravenous drip he received the following: First day, lactate—potassium chloride—sodium chloride mixture, 625 Gm.; 5 per cent glucose, 390 Gm.; blood 60 c.c.; plasma 50 c.c. Second day, lactate—potassium chloride—sodium chloride mixture, 587 Gm.; 5 per cent glucose, 557 grams; blood 50 c.c. Third day, lactate—potassium chloride—sodium chloride mixture, 577 Gm.; and 5 per cent glucose, 330 Gm. Fourth day, lactate—potassium chloride—sodium chloride mixture, 506 Gm.; 5 per cent glucose, 318 c.c. Nothing was given by mouth except the last glucose. On the successive days the stools weighed 340, 436, 455, and 151 Gm., respectively. The body weight changed from 5,950 to 6,650 Gm.

Period II lasted for 3 days, from 3:00 p.m. on September 18, until 3:00 p.m. on September 21. The milk mixtures were all made up to 800 c.c. with water and contained 20 calories per kilogram on the first day and 60 on the last two days. About 50 Gm. of stool were lost at the beginning of this period. The final weight of the stools of this period was considered to be 50 Gm. greater than the amount collected. This correction is about 5 per cent of the whole, so it is felt that the lost stool does not make a significant error for the period as a whole. The body weight changed from 6,650 to 6,550 Gm.

Period III lasted for 3.87 days, from 3:00 p.m. on September 21, until noon on September 25. The baby was fed a volume of 800 c.c. with calories at about 90 per kilogram. The weight changed from 6,550 to 7,060 Gm.

TABLE VI. BALANCE IN CASE 6

	SOLIDS								BODY WEIGHT
	Gm.	H ₂ O Gm.	N Gm.	Cl mM	Na mM	K mM	P mM	Ca mM	Kg.
Period I (3.5 Days)									
Intake	75	3,874	0.0	348	428	119.1	0.0	0.0	5.95
Urine		1,149	5.22	50	64	51.8	16.1		
Stools	43	1,387	3.83	152	154	10.8	10.6	1.12	
Balance			-9.05	146	210	56.5	-26.7	-1.12	6.65
Period II (3 Days)									
Intake	281	1,889	4.47	35	26	36.3	33.9	33.9	
Urine		1,110	2.41	5	20	6.7	4.9		
Stools	44	486	1.66	19	58	30.0	22.9	30.4	
Balance			0.40	11	-53	-0.4	6.1	3.5	6.55
Period III (3.87 Days)									
Intake	750	2,530	15.83	97	78	131.5	95.2	88.0	
Urine		590	5.25	45	11	3.5	17.3		
Stools	65	670	2.20	6	20	61.2	52.0	83.5	
Balance			8.38	46	47	66.8	25.9	4.5	7.06

SALIENT FINDINGS OF THE BALANCES

The data show that water, chloride, sodium, and potassium were retained in all cases during recovery from diarrhea. These retentions give a measure of the probable deficits produced by diarrhea. Since the findings vary somewhat in the different patients, attention will be directed to certain facts in each case.

In Case 1, the patient suffered from rather marked acidosis (serum bicarbonate 5.8 mM per liter) due to diarrhea of short duration. Recovery was rapid with no diarrhea in the hospital. During Period I, when he was treated with solutions containing sodium and chloride, 67 mM of sodium and 13 mM of chloride were retained. Serum bicarbonate was normal after the first day. It is surprising, therefore, to find most of the retained sodium was excreted during Period II, while more chloride was retained. Even in Period III, more chloride

TABLE VII. CONCENTRATION PER LITER OF SERUM

CASE	DATE 1945	H ₂ O Gm.	HCO ₃ mM	Cl mM	Na mM	K mM	pH
1	1-18	920	5.8	100	130	7.4	
1	1-19	943	20.8	104	135	4.6	
1	1-20	951	25.0	95	138	4.9	7.38
1	1-22	948	27.2	102	140	6.8	7.35
1	1-25	942	27.6	86	134	5.8	7.40
2	4-18	926	10.2	103	128	6.7	7.08
2	4-20	944	21.6	92	137	5.0	7.49
2	4-23	945	23.7	98	131	6.8	7.51
2	4-27	940	25.0	95	137	7.9	7.40
3	8-20	924	14.6	110	135	5.0	
3	8-22	934	25.5	95	130	3.5	
3	8-25	937	19.2	109	136	5.4	
4	8-21	917	18.3	100	135	5.5	
4	8-23	934	27.3	100	135	3.4	
4	8-27	933	23.3	97	139	4.9	
4	8-30	934	23.0	110	141	4.5	
5	9-4	923	6.7	121	138	4.8	
5	9-8	942	20.5	116	145	4.8	
5	9-13	948	24.3	110	139	6.3	
5	9-17	939	22.2	108	135	6.3	
6	9-14	925	16.6	95	131	3.7	
6	9-18	951	36.4	94	138	4.8	
6	9-21	940	27.5	102	136	4.7	
6	9-25	935	24.4	104	133	4.9	

than sodium was retained. Such balances could not have occurred without acidosis again developing if both sodium and chloride had remained extracellular. The probable course of events is illustrated in Chart 1. Here a little more than one-half of the sodium balance of Period I is shown to have been contained in the intracellular fluids. In the second period there is a reduction of intracellular sodium below the level at the beginning of the study. Loss of intracellular sodium continued during the third period. It will be noticed that the total net loss of intracellular sodium is about two times greater than the estimated normal content. As would be expected from the lack of intake of potassium, there is a negative balance of this cation during Period I. In the chart the loss of potassium is shown to be somewhat greater than would be explained by the negative balance of nitrogen. In Periods II and III, potassium not accounted for by nitrogen storage was retained in amounts equivalent to about 10 per cent of the estimated normal content.

The patient apparently had a moderate deficit of potassium on admission and had transferred a considerable amount of sodium to the intracellular fluids. The initial low concentration of serum bicarbonate is explained chiefly by loss of sodium from extracellular fluids through transfer of sodium to the intracellular fluids, rather than by true deficit of body sodium. Since the transfer was probably connected with the deficit of potassium, the acidosis of the serum was in part due to loss of body potassium. In this case the changes in intracellular phosphorus are negligible. This case is of particular importance, for it demonstrates that treatment of certain types of acidosis with sodium bicarbonate will restore serum concentrations of bicarbonate, but aggravate the disturbance

in intracellular fluids. The disturbance in the cells is a deficit of potassium and excessive retention of sodium, and these changes cannot be corrected until potassium is available.

In Case 2, the patient suffered from a fairly severe acidosis due to diarrhea. Recovery was somewhat slow in this case. The initial serum showed both low bicarbonate and sodium concentrations (respectively, 10 and 128 mM per liter).

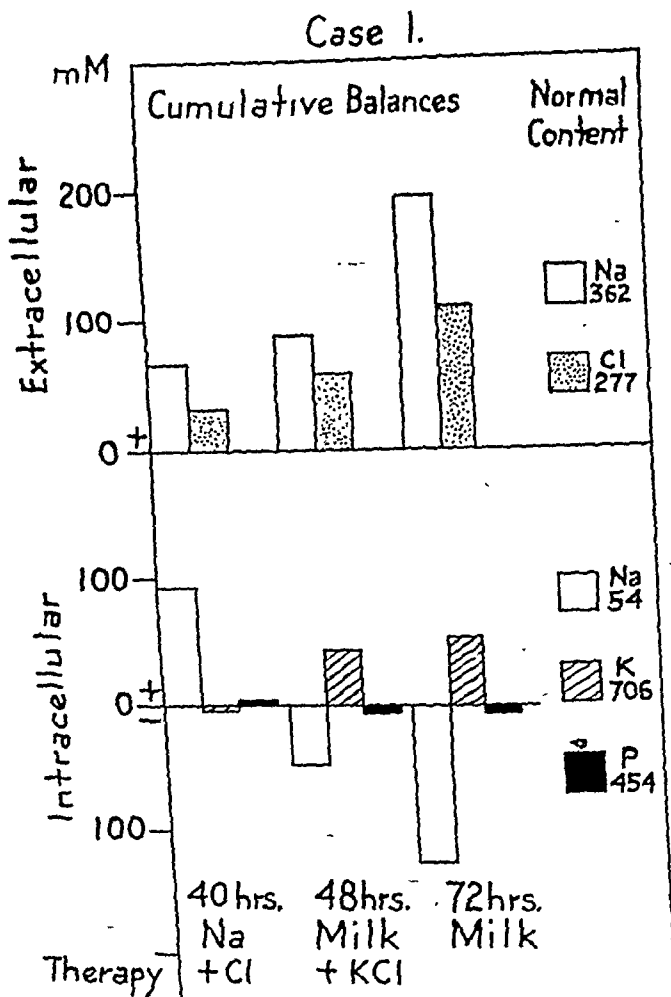


Chart 1.

Subsequently serum electrolyte was approximately normal except for slightly low chloride at the end of Period I, and slightly low sodium at the end of Period II. Correction of the extracellular acidosis is accounted for by the retention of 102 mM of sodium and 55 mM of chloride in Period I. Chart 2 shows that most of the sodium and chloride remained extracellular in Period I. Subsequently both sodium and chloride were excreted in approximately equivalent amounts, but an amount of sodium became intracellular which is about equal to the nor-

mal estimated intracellular content. During the fasting, when no potassium was given, some intracellular potassium was excreted in excess of that accounted for by nitrogen loss. During the last two periods potassium was retained equal to about 14 per cent of the estimated normal content. The changes in intracellular phosphorus are negligible in this patient.

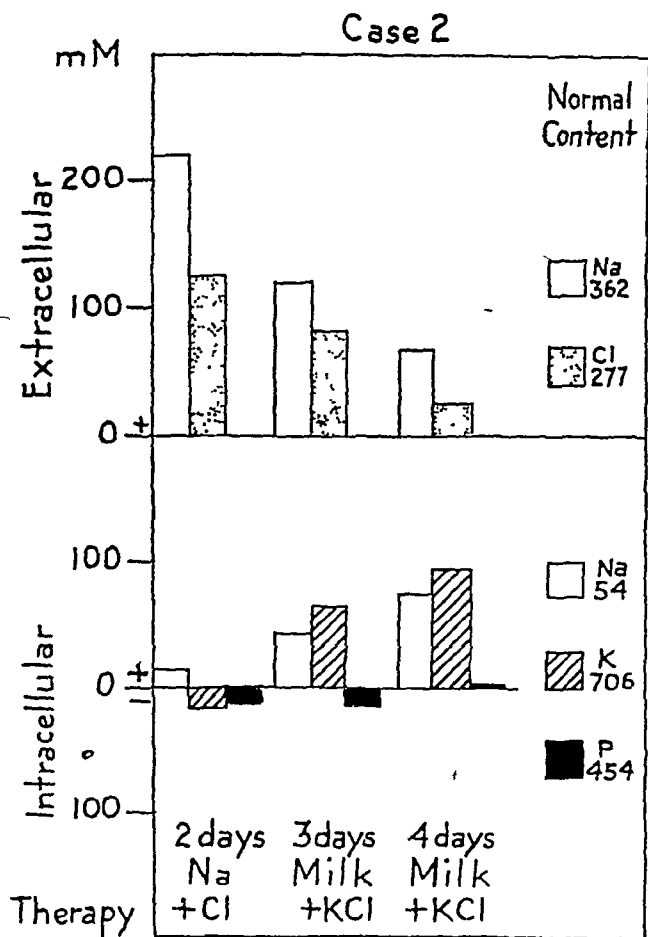


Chart 2.

On admission the acidosis is explained by a deficit of sodium in both intracellular and extracellular fluids. In addition to a deficit of sodium, the intracellular fluids had a considerable deficit of potassium.

In Case 3, the patient suffered from a fairly severe attack of diarrhea which responded somewhat slowly to treatment. The lack of rapid recovery in this case was probably in part due to an attempt to start feeding a little too early. On admission there was only moderate reduction in the concentration of serum bicarbonate (14 mM per liter), essentially normal serum sodium, and high serum chloride (110 mM per liter). Subsequent serum concentrations were

approximately normal except for the slight reduction in serum sodium and chloride at the end of Period I. During fasting and administration of sodium chloride, sodium lactate, and glucose (Period I), about twice as much sodium (93 mM) as chloride (41 mM) was retained. A moderate amount of this sodium became intracellular (Chart 3). During the second period enough sodium was excreted while chloride was retained, to make the final retention of chloride greater than that of sodium (101 mM as contrasted to 35 mM). Chart 3 illustrates that the sodium lost from the cells is about twice the estimated normal content. During the first period, potassium was lost from the cells, but enough

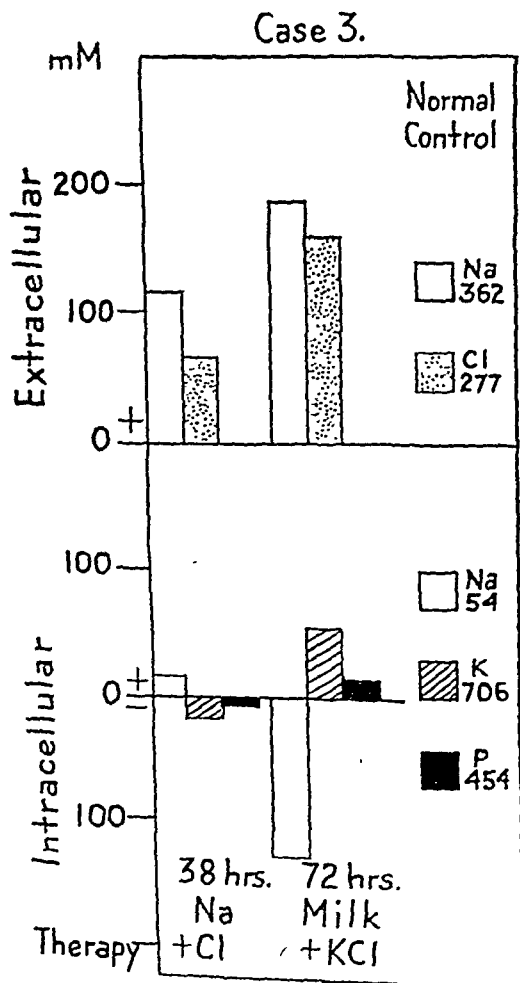


Chart 3.

was retained in the second period to make the final retention of potassium equal to about 11 per cent of the estimated normal content. Appreciable retention of intracellular phosphorus occurred in this patient.

The state of body fluids on admission was much the same in Cases 1 and 3; that is, there was excessive intracellular sodium and a deficit of potassium.

In Case 4, the patient suffered from a severe attack of diarrhea and vomiting which responded slowly to treatment. This patient also was probably fed too soon. On admission, the serum bicarbonate was only slightly reduced; subsequent serum concentrations were approximately normal. During the fasting

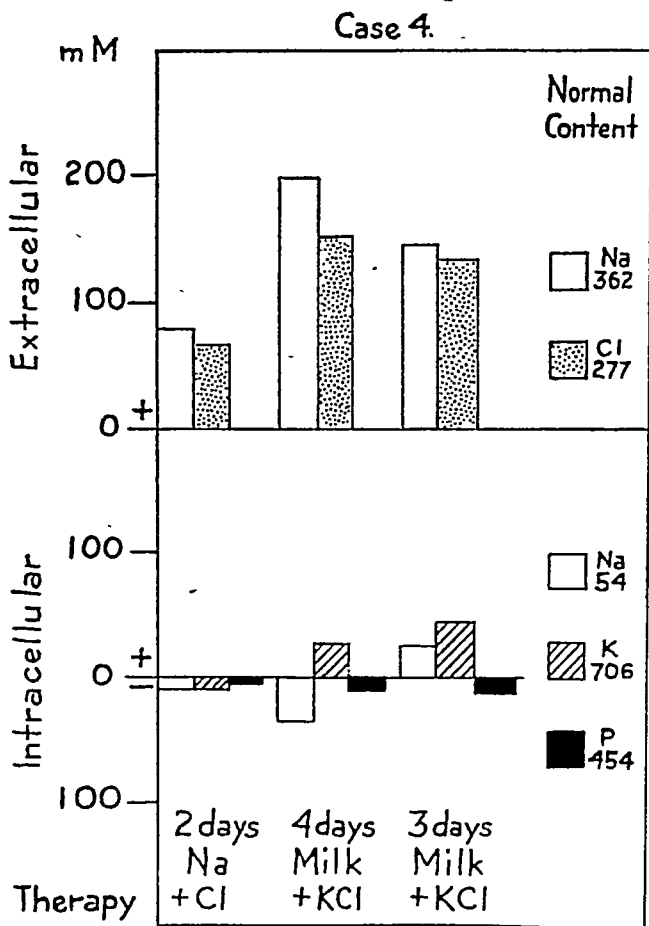


Chart 4.

and administration of sodium chloride, sodium lactate and glucose, the retention of sodium was 85 and chloride, 75 mM. In the second period considerable sodium and chloride were retained. In the last period small amounts of these ions were lost. Chart 4 shows rather small shifts of sodium into and out of the intracellular fluids. Relative to size, this patient retained less potassium than any of the other patients. There was no significant change in intracellular phosphorus in relation to nitrogen.

On admission this patient apparently suffered chiefly from loss of extracellular sodium and chloride, though there was a loss of about 7 per cent of the estimated normal content of potassium. This patient never received adequate calories during the study because his appetite remained poor. This fact and

the apparent lack of satisfactory recovery during the study suggest that a period on adequate calories might have revealed a greater deficit of potassium in this patient. This surmise, however, is not supported by the finding of a relatively high concentration of potassium in the urine of Periods II and III.

Case 5.

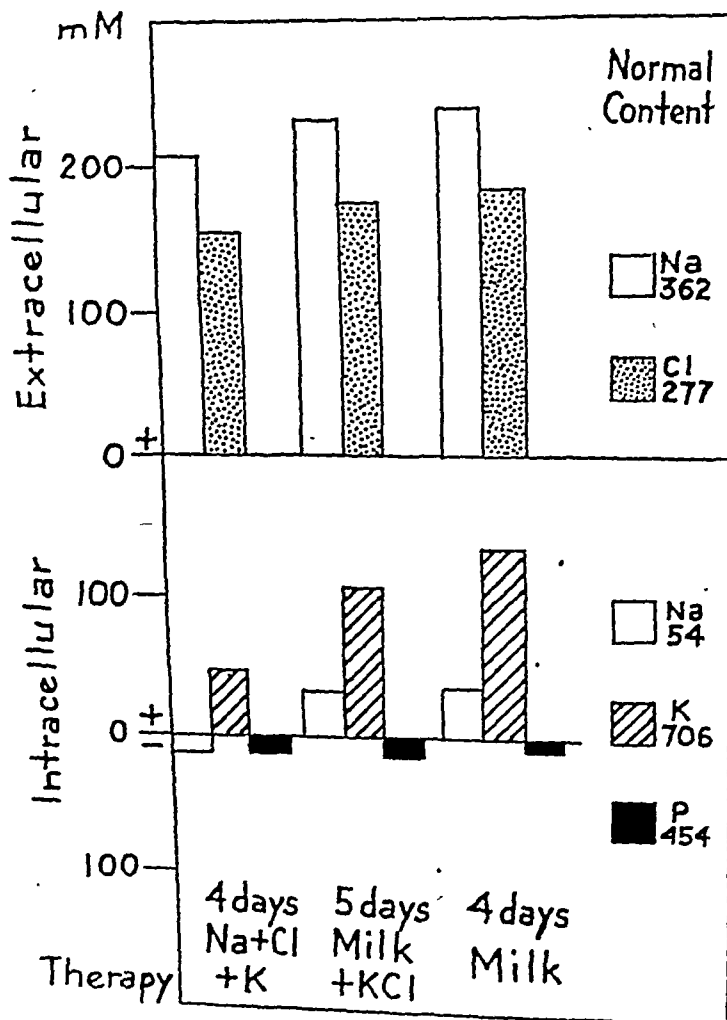


Chart 5.

In Case 5, the patient had suffered for eight days from fever and severe diarrhea and vomiting. He had marked signs of dehydration, acidosis, and shock. Recovery seemed unlikely for three days. While his diarrhea and gastrointestinal disturbances were improved at the end of the study, he required twenty-three days in the hospital to assure proper convalescence.

During Period I, this patient received daily intravenous injections of potassium chloride as well as sodium chloride, sodium lactate, glucose, and blood.

This treatment led to the retention of 106 mM of sodium, 85 mM of chloride, and 15 mM of potassium. These retentions explain the rise in serum bicarbonate from 7 to 21 mM per liter. On admission, serum chloride was 121 mM per liter and it remained high during the entire duration of the study. When food fortified with potassium chloride was given in Period II, a large amount of

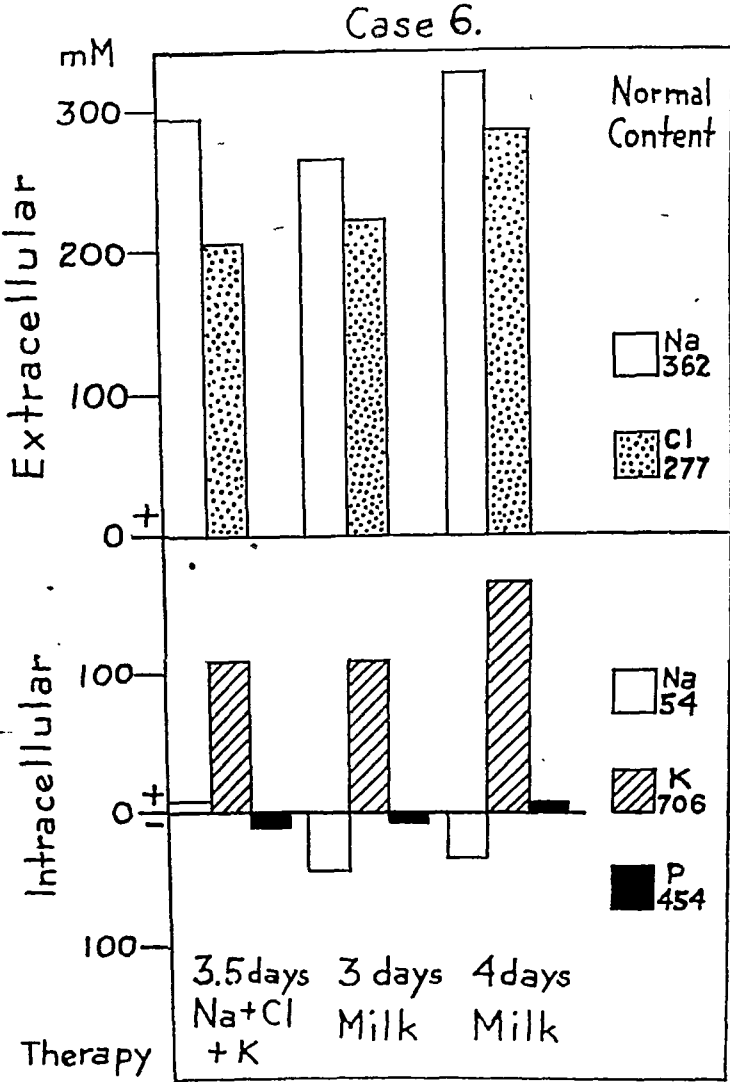


Chart 6.

potassium was retained, together with a considerable amount of sodium and a small amount of chloride. The last period shows chiefly retention of potassium. Chart 5 shows that the sodium and chloride were chiefly retained in the extracellular fluids. The final retention of potassium is equal to about 19 per cent of the estimated normal content. The changes in intracellular phosphorus are negligible.

On admission, the state of body fluids and electrolyte of Case 5 differed from the previous ones chiefly in the magnitude of the deficit of potassium. While there may have been a slight loss of intracellular sodium, no change in intracellular phosphorus was demonstrated.

In Case 6, the patient suffered from severe bacillary dysentery of four days' duration. This patient showed extreme dehydration and fairly marked evidences of shock. As shown in the protocol, he had daily stool volumes equal to almost 8 per cent of the body weight during Period I. Recovery was satisfactory at the end of the study.

During the period of fasting the patient received daily intravenous injections of potassium chloride as well as sodium chloride, sodium lactate, glucose, and blood. When food was started in Period II, no potassium chloride was added to the milk mixture. In Period I, large amounts of potassium, sodium, and chloride were retained. If one takes into account the loss of about 27 mM of potassium which would usually accompany a negative balance of 9 Gm. of nitrogen, the retention of 57 mM of potassium in Period I is quite remarkable. The lack of retention of potassium in Period II is dependent on the increase in stool potassium. Since potassium was retained in Period III, it would probably have also been retained in Period II, if potassium chloride had been added to the food. It is this finding in Case 6 which indicates that 1 to 2 Gm. of potassium chloride should be added to a day's feeding when less than 70 calories per kilogram are taken. On the other hand, the findings in Period III indicate that, when adequate calories can be tolerated, sufficient potassium will be obtained from the usual milk mixtures.

The final retention of potassium in this case is equal to about 23 per cent of the estimated normal content. The changes in intracellular phosphorus are negligible and the loss of intracellular sodium is about two-thirds of estimated normal intracellular content. On admission to the hospital the change in body electrolyte was a deficit of intracellular potassium and sodium, and a deficit of extracellular sodium and chloride.

DISCUSSION

In the presentation of the data, emphasis was placed on the relation of the balance of nitrogen to the retentions of sodium, chloride, phosphorus, and potassium. There was in each case a deficit of extracellular sodium and chloride which cannot be exactly assayed for reasons that will be mentioned later. Previously, the balances of sodium and potassium have been correlated with the balance of water. The latter system tends to measure the balances of water in terms of some assumed relation of electrolyte concentration to water within the cells. The system used in this paper makes the tacit assumption that if the retentions of phosphorus, potassium, and nitrogen enable the cells to have a normal relationship of these constituents to each other, the correct amount of water will be retained to reconstitute normal cytoplasm. Inspection of the data shows that in every case, but particularly in Cases 5 and 6, the retentions of sodium and potassium are so great that they would lead to high concentration of sodium in the serum if a large part of the intracellular base were not relatively less dissociated than extracellular sodium. This finding confirms previous evi-

dences of variations in the activity of intracellular electrolyte.^{1, 15} The magnitude of this sort of change cannot be measured without more accurate knowledge of body water than the present data give. To correlate the retentions of univalent cations with the changes in body water, assurance of a normal state of body tissues at the beginning or end of a balance study is probably necessary.

In the calculations of the shift of sodium across the cell membranes, the change in extracellular volume is calculated from an assumed volume of extracellular water, the balance of chloride, and the serum chloride concentrations. Within the probable values, the assumed initial volume of extracellular water does not make very much difference in the calculated shift of sodium if the balances of sodium and chloride are large. However, the relative change in volume of extracellular water depends on the initial volume of extracellular water and hence such calculations require an accurate measurement of the extracellular volume in order to have validity for predicting intracellular changes in concentration.

The data of this paper do not show directly which tissues account for the deficit of potassium. However, such large deficits as were demonstrated must involve the muscle, since no other tissue has sufficient mass to account for the changes. The importance of changes in muscle composition is substantiated by experimental work which shows that the liver does not undergo loss of potassium in animals receiving diets low in potassium or injections of desoxycorticosterone acetate.^{4, 7} Similar animals showed low potassium in the heart^{4, 5} and the brain.¹⁶ In the demonstrated shifts of sodium, muscle also plays the leading role, since substitution of sodium for potassium has been demonstrated only in muscle and heart tissue.⁴ The liver loses potassium and gains sodium in shock,¹⁷ but this is probably not the same type of change as has been described in a deficit of potassium in muscle. Whatever changes are taking place in other tissues, skeletal muscle accounts for a large part of the loss of potassium and most of the evidences of shift of sodium into and out of the intracellular fluids.

Although Tobler's¹⁸ analyses of muscle in babies dying of diarrhea do not agree in absolute values with modern analyses, they indicate a reduction of 30 per cent of the potassium. The author has analyzed several samples of muscle from babies dying of diarrhea, some of the samples showed a decrease in potassium in relation to fat-free solids equal to about 40 per cent of the normal content. Some of the tissues showed high intracellular sodium, but most of the samples did not. Loss of 40 per cent of the muscle potassium is sufficient to account for the deficits demonstrated in Cases 5 and 6.

The tissue analyses of babies dying of diarrhea showed decreases in muscle phosphorus in some cases equal to 20 per cent of the normal content and usually equal to 10 per cent. It is surprising, therefore, to find that the metabolism studies did not show retentions of intracellular phosphorus during recovery. The phosphorus deficits found in the autopsy material may represent a late stage in the depletion of intracellular electrolyte. Guest and Rapoport¹⁹ reported changes in phosphorus compounds in the red cells in acidosis and advised the use of phosphate in the treatment of acidosis. While the metabolic data do not demonstrate that a deficit of phosphorus is of great importance in diarrhea,

further study may show that therapy directed toward minimizing the loss of phosphorus is indicated.

The charts show rather large retentions of sodium and chloride at the end of the balance periods, in all cases except Case 2. Experimental work²⁰ on cats and dogs showed that the clinical picture of marked dehydration was produced when about one-third of the extracellular electrolyte was removed, and that loss of about one-half of the extracellular electrolyte was as much as an animal could survive. The retention of sodium was more than one-half the estimated content in Cases 5 and 6 and about one-half in Cases 1 and 3. Overexpansion of the extracellular fluids was almost certainly produced in Cases 5 and 6, and probably in Cases 1 and 3. In none of the cases did pitting edema appear, but puffiness about the eyes developed transiently in all but Case 2. Because of the tendency to retention of sodium chloride, the present technique would be difficult to use to demonstrate the actual magnitude of the deficits of extracellular sodium and chloride on admission. From a therapeutic point of view, moderate overexpansion of extracellular fluids is probably harmless and is certainly less dangerous than under-replacement of sodium and chloride.

The data are striking in that they demonstrate that the loss of nitrogen is rapidly restored. During the fasting (Period I), relatively large amounts of nitrogen were excreted, particularly in Case 6; loss of nonprotein nitrogen may account for part of this loss. The rate of excretion of nitrogen diminished markedly in the second period when submaintenance feedings were given. With the exception of Case 4, in which maintenance calories were not taken during the study, in all cases the deficit of nitrogen developing during treatment was restored by the end of the period of observation. This finding is surprising because a positive balance appears almost as soon as milk is given even at a low calorie intake (particularly Cases 1 and 3). While it might be argued that more rapid recovery would be produced by intravenous injection of amino acids, restoration of nitrogen is quite rapid as soon as food is taken. On the other hand, the data do not show how great a deficit of nitrogen had developed before the patients entered the hospital. The data suggest that the importance of such a deficit should be demonstrated before one is justified in administering amino acids intravenously, if this procedure is to interfere with replacement of water and electrolyte. Such will be the case if thrombosis or febrile reactions are produced by injection of amino acids.

From the point of view of therapy, the present study emphasizes the losses of nitrogen, sodium, chloride, and potassium. However, it is chiefly the loss of potassium that takes on new significance since its magnitude is brought into view and the possibility of restoration without food is demonstrated.

Actually the demonstration of the loss of potassium as well as sodium and chloride in diarrhea is not new. In 1850, Schmidt²¹ showed that loss of water, sodium, chloride, and potassium occurred in cholera and dysentery. His terminology and grasp of the problem were so sound that it is surprising that his work was not followed by the development of modern concepts of the physiology of water and electrolyte. Steinitz²² demonstrated that the acidosis of diarrhea was due to loss of more fixed base than acid. Meyer²³ showed that a baby developing rapid decrease in body weight owing to diarrhea lost considerable amounts of

sodium and potassium. His data show that the loss of potassium is greater than can be accounted for by the loss of nitrogen. Tobler¹⁸ showed that the muscle of babies dying of diarrhea had low concentrations of potassium. By analysis of the tissues of puppies dying following experimental diarrhea, Tobler²⁴ showed that most of the water loss was sustained by subcutaneous tissues and muscle. These tissues accounted for most of the loss of sodium and potassium. The losses of electrolyte were roughly proportional to the losses of water—chloride and potassium showing the closest parallelism. Nitrogen was not lost as rapidly proportionately as water, sodium, chloride, and potassium. Tobler appreciated that the tissues were not breaking down as a unit, but thought that the losses of potassium and water indicated a fundamental disintegration of the cells. Jundell,²⁵ while working in Finkelstein's clinic, determined the balances in mild and severe diarrhea. He related the losses of sodium, chloride, potassium, and nitrogen to each other and to the composition of muscle. He realized that potassium was being lost at a greater relative rate than nitrogen, but thought this was probably due to failure of the kidneys to eliminate nitrogen. The losses of potassium in his patients were not as great as in Meyer's²³ patient or in Cases 5 and 6. Meyer's study illustrates the reversal of the losses while recovery occurred in a baby receiving human milk. If emphasis had been placed on the fact that the retention of potassium preceded the retention of sodium and chloride, other studies would doubtless have been made to evaluate this observation and deduce its therapeutic significance.

Thus the great school of pediatrics in Germany which culminated under the leadership of Czerny and Finkelstein appreciated that loss of alkali was an essential feature of malignant diarrhea and that potassium was lost in relative excess of nitrogen. They conceived of the rapid terminal loss of nitrogen as a consequence of the loss of alkali. In this assumption they may have been correct, but they were not correct in assuming that the process could not be reversed by specific replacement therapy.

Holt, Courtney, and Fales²⁶ showed that the loss of potassium in diarrheal stools is greater than can be accounted for by the loss of nitrogen. That Holt appreciated the implications of these findings is indicated by the following quotation: "In attempting to supply this loss by hypodermoclysis it should be remembered that not only are water and sodium needed, but potassium and magnesium as well. With these facts in mind, a better solution for use in hypodermoclysis can certainly be devised than normal saline or than Ringer's solution." Holt, Jr.,²⁷ reported additional data obtained by his father and was impressed by the same findings, for he wrote: "A comparison of potassium and nitrogen retentions shows that loss of potassium is seldom accompanied by a proportionate loss of nitrogen and may even be accompanied by a retention of nitrogen. The conclusion to be drawn from this is that intracellular fluid may be lost without death of the cells. Hitherto, attention has been directed only to the replacement of plasma electrolyte and that of interstitial tissue fluid. The question of replacing intracellular fluids appears of equal importance and should by no means be neglected."

Butler, McKhann, and Gamble²⁸ reported data essentially like those of the present paper except for omission of chloride balances. Again a quotation in-

icates appreciation of the significance of the findings: "The presence of an intracellular fluid loss complicates our conception of the process of dehydration and disturbs our confidence in the therapeutic adequacy of parenteral treatment. Since repair solutions must be placed in the vascular or in the interstitial compartment, they cannot contain with safety the intracellular materials, such as potassium and phosphate, at concentrations above the small values prescribed for them in extracellular fluids. The solution devised by Hartmann contains potassium appropriately to this extent. It is evident, however, that such solutions cannot provide an adequate replenishment of intracellular materials. Parenteral therapy has a large, often dramatic, effectiveness. It must be admitted, however, that it is not always successful and it may be hoped that recognition of an additional pathologic process in the situation will eventually produce supplementary measures which will provide a more complete control of the severe stage of diarrheal disease."

These quotations raise the question of why adequate amounts of potassium were not given. The German students sought to treat diarrhea largely by providing some food which would change the character of the stools from diarrheal to "dyspeptic"; that is, from stools containing large amounts of sodium and potassium to ones containing little alkali and large amounts of calcium and magnesium soaps. In this they were partially successful as indicated by the survival of Finkelstein's protein milk. They appreciated that subcutaneous saline produced considerable improvement, but felt that if the stools remained watery a relapse into a worse state would occur. Because of this attitude the possibilities of replacement therapy were never adequately explored in Germany.

In this country, replacement therapy has been quite thoroughly tried, usually guided by chemical examination of the blood. In fact, restoration of normal plasma electrolyte has seemed so desirable that this end has been sought even though clinical signs and other evidences have indicated that normal serum concentrations do not restore the functions of a child who has suffered from dehydration due to diarrhea. The very success of some of the therapeutic procedures seems to have diverted pediatricians' attention from the importance of loss of potassium.

The use of large quantities of physiological saline by intraperitoneal injection produced a gratifying decrease in the mortality. While this route has been largely abandoned in favor of subcutaneous and intravenous therapy, Blackfan and Maxey's²⁹ work showed that diarrheal patients need large amounts of sodium chloride. The demonstration of serum acidosis by Howland and Marriott,³⁰ and Schloss and Stetson³¹ was accompanied by proof that the acidosis could be corrected by the intravenous injection of sodium bicarbonate. However, the improvement in the symptoms of acidosis and the restoration of the concentration of blood bicarbonate seemed to both groups of workers to raise false hopes that were not fulfilled by a decrease in mortality. The original reaction to the use of sodium bicarbonate is confirmed by the high mortality of Hartmann's patients who were given large amounts of sodium lactate and in whom restoration of serum bicarbonate was used as a criterion of successful treatment.⁴¹ Several papers³²⁻⁴¹ have shown the nature of the disturbances in serum concentrations

and made various recommendations for treatment. Powers⁴² introduced the use of transfusions and correctly pointed out that the indication for transfusions is shock and only secondarily, anemia. He described a form of treatment which combined most of the contemporarily accepted procedures. The outline emphasizes the use of fasting followed by small feedings, intraperitoneal injection of physiological saline, and intravenous glucose and blood transfusions. The mortality records of this series suggest that these procedures accomplished as much as any of the more recent modifications using constant intravenous injections and precisely calculated doses of sodium bicarbonate or sodium lactate.⁴¹

Ultimately, the failure to use potassium salts parenterally was apparently connected with two ideas. First, it was realized that a rise in the concentration of potassium in plasma could produce death by stopping the heart. Second, cellular membranes were considered to be relatively impermeable to cations and hence loss of potassium was considered to be caused by some fundamental change within the cells. As indicated in the introduction, the second surmise is no longer tenable and recent studies have shown that the dangers of potassium poisoning, although real, are not as great as might be anticipated.

Heart block is produced when the serum concentration of potassium reaches a level of 10 to 12 mM per liter.⁴³ The disturbance in the heart is connected with the rise in extracellular concentration and not directly associated with a rise in the intracellular potassium of the heart.⁴⁴ In the parenteral injection of potassium salts, the rate of administration must be slow enough not to lead to a temporary rise to toxic levels and the total dose must not be large enough to lead eventually to a toxic extracellular concentration.

When potassium chloride is injected intravenously, the serum concentration increases as if potassium were distributed equally throughout body water.⁴⁵ Actually it is known that the liver and heart take up relatively more potassium than other tissues when the serum concentration increases.⁴⁶ Temporarily the muscle content can increase 5 to 8 per cent above the high normal level.⁶ Since the intracellular water of the muscle makes up about 70 per cent of the total intracellular water, such an increase can amount to about 4 mM of potassium per kilogram of body weight and about one-half of this rise may occur before the serum concentration reaches 10 mM per liter. The kidneys are capable of excreting potassium in a concentration of over 100 mM per liter so that a dangerous rise in potassium concentration is unlikely to develop as long as urine is being excreted. During the period of fasting, the first four cases showed urine concentrations of potassium varying from 11 to 30 mM per liter and excreted 2 to 5 mM of potassium per day in the urine. In Cases 5 and 6, the concentrations were 68 and 45 mM potassium per liter, and the daily urinary excretion 8.5 and 6 mM, respectively. Thus the parenteral potassium did not produce unusual urinary concentrations. The transfer of potassium to the cells explains this finding. Miller and Darrow⁶ showed that the toxic dose of potassium chloride injected into the peritoneal cavity is about twice as large in rats with a deficit of muscle potassium as in normal rats. The resistance to potassium poisoning was explained by a rise in muscle potassium accompanying injections of potassium chloride.

Bearing these facts in mind, one can predict with reasonable certainty the safe dose of potassium for intravenous or subcutaneous use. If the concentra-

tion of serum potassium is 5 mM per liter, a rise in concentration of 4.5 mM will not produce heart block. Assuming equal distribution throughout body water, 3.1 mM of potassium per kilogram of body weight will produce a rise of 4.5 mM in the concentration of serum potassium. If injected slowly, this amount of potassium should be safe for the treatment of diarrhea unless the serum concentration is already high and urine is not being formed. Injection over a period of four to eight hours should assure equal distribution of injected potassium and avoid a sudden rise in the serum concentration.

In the practical choice of a solution for parenteral use, the safe dose of potassium was added to quantities of sodium chloride and sodium lactate suitable for replacing extracellular electrolyte. Darrow and Yannet^{1, 20} showed that from one-third to one-half of the extracellular electrolyte must be removed to produce the picture of advanced dehydration. This amount of electrolyte is contained in 80 to 100 c.c. of physiological saline per kilogram of body weight. Since a greater amount of sodium than chloride is desirable, sodium lactate was included. The concentrations used in this study were approximately: potassium chloride, 40; sodium chloride, 100; and sodium lactate, 50 mM per liter. Such a solution can be made by adding 40 c.c. molar sodium lactate, 2 Gm. potassium chloride, and 3 Gm. sodium chloride to 710 c.c. of water. The sodium chloride and potassium chloride can be sterilized separately and added, together with one 40 c.c. ampule of molar sodium lactate, to 710 c.c. of sterile water. This solution is not irritating when given subcutaneously and will not produce potassium intoxication in the recommended doses given over a period of four to eight hours.

Untreated patients suffering from the dehydration of diarrhea may have a high concentration of potassium in the serum. In Case 6, the serum concentration was slightly low (3.7 mM per liter) while in the other cases the potassium concentration was slightly high on admission (4.8 to 6.7 mM per liter). However, the author has found levels as high as 10 to 12 mM per liter in moribund diarrheal patients. This finding suggests that the poor circulation of the terminal stages tends to lead to loss of potassium from the cells, in spite of a deficit of potassium in intracellular fluids. This finding is in agreement with recent data on shock produced by tourniquets.⁵³ Hence in moribund patients and perhaps in all cases of severe diarrhea, infusions of physiological saline and glucose solutions should be initiated for an hour or until urine formation is assured, and then the solution containing potassium chloride can be started.

In Cases 5 and 6, and in the series reported elsewhere,⁵¹ treatment was carried out with the solution containing potassium chloride as well as sodium chloride and sodium lactate. In severe dehydration, the initial deficit of sodium and chloride should be replaced by 80 to 100 c.c. of such a solution, and at the same time potassium will be given at a safe rate. The solution will have to be injected repeatedly as long as the diarrhea continues and parenteral fluids are given. When submaintenance feeding is started, retention of potassium will be promoted if 1 to 2 Gm. of potassium chloride are added to the food each day. When maintenance feeding can be taken without inducing watery stools, no potassium chloride need be added to the food.

The present work shows that failure to give potassium is a factor in the untoward results obtained previously. The reduction in concentration of serum potassium is probably one of the untoward effects of the usual therapy. Considering 4 mM per liter the low normal level of potassium in serum, the cases illustrate this difficulty. At the end of Period I, the serum potassium concentration was below 4 mM per liter in Cases 3 and 4, but not in Cases 1, 2, 5, and 6. In Case 1, there was no diarrhea in the hospital and in Cases 5 and 6, potassium was given in Period I. Increase in intracellular sodium may be a second untoward effect of the usual replacement therapy. In Case 1, considerable sodium entered the cells and explains why a large retention of sodium and a small retention of chloride raised the serum bicarbonate no higher than normal. Elsewhere¹³ the bearing of a deficit of the intracellular sodium on the dose of sodium bicarbonate necessary to restore the serum bicarbonate in acidosis is discussed. It is obvious that the dose of sodium bicarbonate might be quite enormous if sodium is transferred to the intracellular fluids to replace all of a large deficit of potassium in the cells. The present data show that the deficit of potassium may be equivalent to one-half of the estimated extracellular sodium of the body (or one-quarter of the estimated potassium of the body) and that substitution of sodium for the deficit of potassium is likely if bicarbonate therapy is pushed. If a high intracellular sodium concentration is harmful, aggravation of this type of change in the cells is undesirable. More research into the consequences of this phenomenon must be made before its role in the untoward effect of therapy with sodium chloride and sodium bicarbonate can be decided. It suffices here to state that the treatment of acidosis should not be undertaken without considering the effect on the cells; probably the use of the salts of both sodium and potassium is usually indicated in other types as well as in diarrheal acidosis.

Actually it is known that certain functions are affected by a deficit of potassium. Familial paralysis⁴⁷ is accompanied by a low concentration of serum potassium and similar paralysis has been observed in dogs having low serum potassium as a result of injections of desoxycorticosterone acetate.⁷ It is unlikely that this type of reaction develops in untreated diarrheal patients, since untreated cases are apt to have high serum potassium concentrations. After treatment with sodium and chloride, such an occurrence is a possibility. Meyer and Nassau⁴⁸ emphasized that loss of muscle tone is an invariable accompaniment of severe diarrhea. Deficit of muscle potassium is probably associated with this phenomenon. Diets low in potassium and repeated injections of desoxycorticosterone acetate produce myocardial necrosis in experimental animals.^{49, 50, 4} Myocardial failure is the usual sign of overdosage with desoxycorticosterone acetate.⁵⁰ One of the most ominous signs in diarrhea is a slow heart rate. Further study may show that the heart symptoms in diarrhea are dependent in part on a deficit of potassium. Thus, nervous, muscular, and cardiac disturbances can be produced by a deficit of potassium, but further study will be necessary to differentiate the disturbances associated with a deficit of potassium from those produced by a loss of sodium, chloride, and water.

Elsewhere⁵¹ a modification of present methods of treating diarrhea is described. Although the only significant change is the parenteral administration

of potassium, the method lowered the mortality rate from 25 per cent to about 5 per cent. Harrison, Tompsett, and Barr¹² observed improvement in two adults suffering from fatty diarrhea when they were given potassium by mouth. These authors correctly concluded that the finding of a low concentration of potassium in serum indicated that potassium may be lost so rapidly in diarrheal stools as to lead to a deficit of body potassium and that this deficit can be reversed by giving potassium salts.

SUMMARY

Balances of nitrogen, sodium, chloride, potassium, phosphorus, and calcium are reported during recovery from dehydration due to severe diarrhea. The balances are correlated with each other to bring into view the disturbances in composition of the intracellular as well as the extracellular fluids.

Diarrhea led to a decrease in extracellular water owing to loss of sodium and chloride in extracellular fluid. In some cases, a large part of the loss of extracellular sodium was explained by transfer of sodium from the extracellular to the intracellular fluids. Such a transfer of sodium explained the acidosis in one case. In other cases, sodium was lost from the intracellular as well as extracellular fluids.

Loss of intracellular potassium was a prominent feature of all cases and was equivalent in two cases to about one-fourth of the estimated normal potassium content of the baby. This loss of potassium is in excess of the loss which would be expected from loss of nitrogen.

No great disturbance in the relative concentration of intracellular phosphorus was demonstrated.

The usual replacement therapy of fasting and the parenteral administration of solutions containing sodium chloride, sodium lactate, and glucose corrected the extracellular concentrations. However, considerable sodium entered the cells in two cases and loss of potassium was aggravated.

Replacement of intracellular potassium was obtained by adding 1 to 2 Gm. of potassium chloride to submaintenance feeding. One observation indicated that replacement of intracellular potassium is not likely to occur if the diarrhea continues and submaintenance milk feedings without added potassium chloride are given. The data indicate that the usual milk mixtures contain sufficient potassium to replenish the tissues if these mixtures can be taken in the amounts necessary for growth.

During the period of fasting, retention of intracellular potassium can be produced by adding potassium chloride to solutions containing sodium chloride and sodium lactate. Such a treatment restores extracellular concentrations and replaces the deficit of potassium in part. Accompanying this replenishment of both intracellular and extracellular electrolyte, the babies looked better than after the usual type of treatment and recovered from attacks of diarrhea that would usually be fatal.

The significance of a deficit of potassium is discussed.

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THE USE OF POTASSIUM CHLORIDE IN THE TREATMENT OF THE DEHYDRATION OF DIARRHEA IN INFANTS

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THE comprehensive plan for the treatment of diarrhea published by Powers in 1926,¹ apparently produced as satisfactory results as any of the more recent systems. The later papers have advocated substitution of subcutaneous or intravenous injections of essentially the same solutions containing sodium chloride, sodium bicarbonate (or sodium lactate), and glucose in place of the intraperitoneal injections recommended by Powers. The dose of bicarbonate necessary to restore the concentration of serum bicarbonate has been more precisely defined.² However, the mortality records do not show that these refinements improve the final result. For all practical purposes no fundamental, new principle in the treatment of diarrhea has been introduced in the last twenty years.

In an accompanying report,³ the magnitude of the loss of body potassium was shown to be equivalent to about one-quarter of the estimated body potassium in the most severe cases. Furthermore, it was demonstrated that this loss of potassium is not accounted for by disintegration of the cells as a whole; that is, the deficit of potassium was not accompanied by a corresponding loss of nitrogen and intracellular phosphorus. During the period of fasting, when all fluids were given parenterally, retention of potassium unaccompanied by a positive balance of nitrogen and intracellular phosphorus was produced by the addition of potassium chloride to the solutions in general use for the replacement of body water and electrolyte. These findings have formed the basis for the development of a new system of treatment which is described in the present paper. The results obtained by the new treatment are contrasted to the results obtained by the previous method.

The procedures used in the therapeutic trial cannot be precisely described. As in any type of treatment of diarrhea, the therapy varied a great deal as a result of varying severity of the symptoms, degree of dehydration, and the response of the diarrhea to treatment. In addition, the procedures used at the end of the study were the result of experience obtained earlier in the experimental trial. In other words, the system of treatment was a result of the information obtained with the new therapeutic agent during a therapeutic trial of its effectiveness. The following outline shows the general plan of treatment.

1. *Initial Treatment of Shock.*—On admission, in severe cases the patients received an intravenous injection of whole blood or plasma (10 to 20 c.c. per kilogram of body weight), together with an equal volume of physiological saline. This procedure sought to improve the circulation so that oliguria was

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overcome and a partial restoration of the functions of the enzyme systems of the cells would be obtained. Since it is not always possible to recognize the symptoms of shock* as distinguished from dehydration, transfusions were given in all severe cases before, rather than after, the development of obvious shock. In milder cases only saline and glucose intravenously were given for this purpose.

2. *Period of Fasting.*—Oral administration of food and water was withheld until all evidence of dehydration was overcome, nausea was no longer manifest, and intestinal functions had been partially restored. During this phase all fluids were given parenterally by slow intravenous injection, supplemented by subcutaneous injections in many cases. Nothing was given orally to any infant during the first twenty-four hours and a few infants received nothing by mouth for six days.

3. *Replacement of Body Water and Electrolyte.*—During the first twenty-four hours replacement of most of the deficit of body water and electrolyte was attempted by the subcutaneous or intravenous injection of from 80 to 150 c.c. per kilogram of body weight of a mixture of potassium chloride, sodium chloride, and sodium lactate (this mixture will be called potassium chloride-sodium chloride-lactate mixture and is described later). The rate of injection varied; it was given as rapidly as 2 c.c. per minute over a period of four hours; usually the estimated dose was given in from eight to twelve hours by slow drip. During this initial period of electrolyte replacement, enough 5 per cent solution of glucose was injected intravenously to make the total water intake from 150 to 280 c.c. per kilogram of body weight.

4. *Maintenance of Body Water and Electrolyte.*—After the first day, smaller amounts of the potassium chloride-sodium chloride-lactate mixture (from 20 to 50 c.c. per kilogram of body weight) were given daily as long as the stools remained watery. In addition, sufficient 5 per cent solution of glucose was injected intravenously to make the total fluid intake from 150 to 200 c.c. per kilogram of body weight. In some cases these glucose and electrolyte solutions were injected subcutaneously in a mixture of one-half potassium chloride-sodium chloride-lactate solution and one-half 5 per cent glucose.

In a few cases, a mixture of amino acids (Mead Johnson and Company) was added to the other fluids without obvious changes in the course as compared with those receiving no amino acids.

5. *Vitamins.*—Upjohn's Solu-B was added to the glucose solutions in the majority of cases. All patients were given intramuscularly 1 c.c. injections of crude liver extract twice a week.

*It is realized that the term shock is unsatisfactory since it has been applied to a number of conditions not clearly related to each other. In this paper the authors refer to evidences of permanent damage to the functions of the cells which develop as a result of diarrhea. Dehydration or deficit of body water and electrolyte does not mean the same thing, although eventually it leads to shock in this sense of the word. When the circulation is reduced for a sufficient period, secondary changes take place within the cells probably owing to anoxia. These are made manifest in the liver by failure of certain enzymes⁴ and in the muscle by changes in the distribution of electrolyte.⁵ It is probably failure of these cellular functions, rather than failure of the circulation, which explains the so-called irreversible stage of shock. At present, improvement of the circulation has been the most effective means of preventing and, to a certain extent, reversing the changes in cellular functions. In shock due to electrolyte deficit, restoration of body electrolyte is an essential part of the treatment, but plasma or blood makes electrolyte therapy appreciably more effective.

6. *Feeding.*—Food was started when the stools were no longer watery and all evidence of dehydration had been overcome. The period of fasting varied from one to six days. The food was milk with 2 per cent fat and 5 per cent dextrimaltose. The milk was made from powdered whole lactic milk and powdered skimmed milk restored to their original concentrations with water. Equal parts of these two reconstituted milks formed the basis of the food. During the first day after resumption of feeding, 10 calories per kilogram of body weight were offered. In most of the cases, the food was diluted with sufficient water to give 150 c.c. of fluid per kilogram of body weight per day. If the infant failed to take this amount of food, the fluid intake was supplemented by subcutaneous or intravenous injections of physiological saline or 5 per cent glucose. The feedings were increased gradually over a period of from seven to fourteen days until full feedings were taken.

Beginning in October, from 1 to 2 Gm. potassium chloride were added to each day's feeding when the caloric intake was less than 70 per kilogram of body weight.

Before instituting this treatment, essentially the same procedures had been carried out except (1) only physiological saline or a mixture of about two parts physiological saline with one part isotonic sodium lactate was used, and (2) no liver extract was used. One of the authors (D. C. D.) has used liver extract for years, but had never observed a definite beneficial result such as will be demonstrated when the series treated with potassium chloride-sodium chloride-lactate mixture is contrasted to the series receiving no parenteral potassium.

When the first patients received potassium intravenously, the clinical response was so striking that it was decided that it was important to obtain as wide an experience with the therapy as possible. For this reason all patients suffering from diarrhea received some form of potassium therapy after September. Hence there are no control cases coming at the same time of the year. However, from June to September about the same number of cases had been treated by the conventional therapy as were treated by the new method from September to November.

All the patients treated for diarrhea were babies brought to the Harriet Lane Home because of a chief complaint of diarrhea. All patients were seen (C. D. G.). Owing to limitation of the number of beds, only severely ill infants were admitted to the wards. As a result, the patients studied were only those infants who were thought unlikely to recover unless treated in the hospital. The clinical impression was that both groups were roughly comparable in degree of severity of the illness. The ages of the two groups were essentially the same. Thirty-eight of the control and forty-three of the infants treated with potassium were under 6 months of age. Of the patients receiving potassium therapy, 18 per cent showed either Flexner bacilli or *Proteus morganii* in the stools. The proportion of dysentery cases in the control group cannot be stated, because the stool cultures were not taken in as satisfactory a manner.

The reader is referred to Cases 5 and 6 of the accompanying paper³ for the details of the course in two extremely sick infants treated with potassium.

Chart 1 shows the number of cases in the control and experimental groups, together with the mortality. In the control series, six cases must be excluded because their deaths were associated with the following conditions in addition to diarrhea: (1) Sepsis due to alpha streptococcus, to *Escherichia coli*, to *Bacillus pyocyaneus*, and to hemolytic *Staphylococcus aureus*; (2) prematurity in two infants weighing less than 1,300 Gm. The corrected mortality of the control series is, therefore, 17 of 53 cases. The records of the 17 fatal cases reveal nothing characteristic. The deaths occurred at varying intervals after therapy was started and the manner of exitus showed no characteristic features.

PATIENTS TREATED FOR ACUTE NUTRITIONAL DISTURBANCES

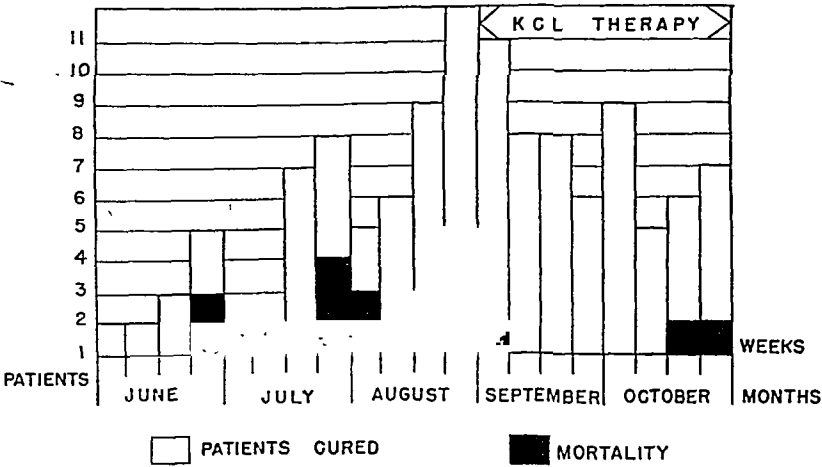


Chart 1.

In the group treated with potassium, one patient died of sepsis due to *B. pyocyaneus* as revealed by a heavy growth in the culture taken from the blood on admission. This organism was grown in practically pure culture from the infant's intestines and at autopsy, ulceration of both the small and large intestine was found. The premature infant listed in Table I weighed 1,300 Gm. and died thirty-six hours after entering the hospital and receiving potassium therapy. Excluding these two cases, the corrected mortality in the cases with potassium therapy was 3 of 50 patients.

The three fatal cases of the potassium series are of interest. The first death occurred in an infant, aged 5 months. The baby showed marked dehy-

TABLE I. MORTALITY IN DIARRHEA

	CONVENTIONAL THERAPY	POTASSIUM THERAPY
Total patients	59	52
Deaths with sepsis	4	1
Deaths with prematurity	2	1
Uncomplicated cases	53	50
Uncomplicated deaths	17	3

dration on admission and died six hours after admission to the hospital. The second death occurred in an infant, aged 25 days. Before admission to the hospital he had had diarrhea for four days. He had been exposed to an epidemic of diarrhea in newborn infants in which four others died. In the hospital, the diarrhea continued for eighteen days. The third death occurred in an infant, aged 3 months, suffering from congenital syphilis as well as diarrhea. The diarrhea had apparently responded satisfactorily to treatment and he received penicillin for the syphilis. The diarrhea had been absent for five days and he was scheduled for discharge the following day. However, he died suddenly and unexpectedly during the night. While he did pass two loose stools during the night, diarrhea was not considered the cause of the death. No autopsy was performed.

Chart 1 shows the mortality per week during the summer. It will be seen that the potassium therapy was instituted during the maximum incidence of diarrhea and at a time when the mortality was high. It is striking to observe that only one of the first forty-two patients treated with potassium died. This favorable record occurred in September, when the mortality from diarrhea is usually high in Baltimore.

COMPLICATIONS OF TREATMENT WITH POTASSIUM CHLORIDE

Potassium Intoxication.—It had been anticipated that potassium intoxication might be encountered. The concentration and total dose of the solution used were calculated to give from 3 to 4 mM of potassium in the maximal amounts recommended for twenty-four hours.³ If none of this potassium were excreted or transferred in unusual amounts to the intracellular fluids, the rise in concentration of potassium in the serum would be 4 to 5 mM per liter. If the initial serum concentration were 5 mM per liter, the final concentration would be just below that producing heart block. The potassium chloride-sodium chloride-lactate solution has the following concentrations:

K	35 mM per liter
Na	122 mM per liter
Cl	104 mM per liter
Lactate	53 mM per liter

It can be made according to either of the following formulas:

I. KCl	2 Gm.	II. KCl	2 Gm.
NaCl	3 Gm.	NaCl	3 Gm.
Molar sodium lactate	40 c.c.	$\frac{1}{6}$ molar sodium lactate	250 c.c.
Water	710 c.c.	Water	500 c.c.

The solutions can be autoclaved or the sodium chloride and potassium chloride can be sterilized by dry heat and added to water, together with one 40 c.c. ampule of commercially prepared molar sodium lactate.

Table II shows the concentrations of potassium in the serum of six patients receiving the potassium chloride-sodium chloride-lactate solution. The concentrations were those obtained from serum taken about two hours after finishing the injection of about 80 c.c. per kilogram of body weight over a

period of from four to eight hours. Three values are moderately elevated, but well below the level associated with heart block (10 to 12 mM per liter). In several patients, normal electrocardiograms were obtained during or within two hours following the injection of potassium chloride-sodium chloride-lactate solution.

TABLE II. EFFECT OF SUBCUTANEOUS INJECTION OF 80 C.C. PER KILOGRAM OF BODY WEIGHT OF POTASSIUM CHLORIDE-SODIUM CHLORIDE-LACTATE SOLUTION

CASE	POTASSIUM CONCENTRATION mM per L. of serum
1	3.74
2	4.00
3	6.87
4	3.40
5	6.75
6	6.54

In one patient, potassium intoxication occurred and almost led to death. The infant, aged 12 days, had had diarrhea for two days before admission. During the first three days in the hospital, the potassium chloride-sodium chloride-lactate mixture was administered parenterally. At this time the diarrhea had ceased and the potassium therapy was discontinued. Feedings were given for the next seven days, and the infant's condition seemed to be improving. However, on the eleventh day, the diarrhea recurred. The potassium chloride-sodium chloride-lactate solution was again injected subcutaneously. Within one hour, the infant became cyanotic owing to heart failure. Complete heart block with a rate of about forty per minute was demonstrated by electrocardiogram. At this time the concentration of potassium in the serum was 12.3 mM per liter. Following an intravenous injection of 15 c.c. of 10 per cent solution of calcium gluconate (Smith's) and 150 c.c. of 17 per cent solution of glucose, the cyanosis disappeared, the heart rate increased, and the circulation improved almost immediately. The electrocardiogram was improved one hour later and was normal two hours later. The case will be reported in an accompanying paper.⁶ The cause of the rise in serum potassium is not clear in this case. The potassium chloride-sodium chloride-lactate solution was given immediately on recurrence of the diarrhea in this case and later it was apparent from the chart that the baby had been passing very little urine at this time. Furthermore, this baby probably had no deficit of potassium when the second treatment was started, because the initial treatment and the food had replenished the intracellular fluids, and because the relapse had not been of sufficient duration to induce a second deficit of potassium.

It was the developments in this case in particular that led the authors to institute the treatment of paragraph 1 before starting the potassium chloride-sodium chloride-lactate solution. There are other findings which indicate that parenteral potassium should not be started precipitously. In two patients before treatment, the concentration of potassium in the serum was 7 and 9 mM per liter. In connection with several other patients in New Haven moribund from diarrhea, one of the authors (D. C. D.) has observed equally high concentrations of potassium in the serum. As demonstrated in the metabolism

study and actually found by tissue analysis in some of these cases, the intracellular fluids of all these patients were probably low in potassium. The high concentration of potassium in the serum of patients in the advanced stage of dehydration is probably dependent on two factors: (1) The oliguria accompanying dehydration undoubtedly diminishes urinary excretion; (2) when the circulatory failure reaches the degree causing shock, serum concentration of potassium is apt to rise. This observation has been made repeatedly in shock and a recent study shows that this event occurs owing to a loss of potassium from the tissues.⁵ Thus it is desirable to replenish intracellular potassium, but one must not accomplish this end under conditions leading to a high concentration of potassium in the serum.

The authors do not believe there is a great deal of danger of potassium intoxication following the injection of potassium chloride-sodium chloride-lactate solution if the following precautions are observed: (1) The dose should seldom be over 80 c.c. per kilogram per day; (2) the rate of injection should not be greater than necessary to give the indicated amount in four hours, and from eight to twelve hours should be employed as a rule; (3) evidence of urine excretion should be obtained before starting the injection of the potassium chloride-sodium chloride-lactate solution; and (4) the solution should not be given until the measures employed in shock have produced some recovery in the circulation and the functioning of the enzyme systems of the cells. Recent studies have emphasized that when the anoxia of shock reaches a certain degree, a number of enzymes in the liver cease to function. When this occurs, potassium may be lost from the liver.⁷ Similar events probably take place in other tissues. Hence potassium may not readily be retained in the tissues while the anoxia of poor circulation persists, despite the fact that there is probably a deficit in the intracellular fluids.

Erythema With Desquamation.—Five patients developed striking, generalized erythema on the second or third day of parenteral treatment with potassium chloride-sodium chloride-lactate solution. Three to five days after the erythema, the skin became roughened and desquamated. Otherwise these patients did not appear to differ from the others. No serum potassium concentrations or electrocardiograms were taken on these patients at the time of the erythema. Although the dilatation of the capillaries may have been produced by a rise in the concentration of serum potassium, the exact cause of this phenomenon cannot be stated. In general, the patients receiving potassium show the normal, rosy color of the skin at a time when pallor is the rule when solutions containing no potassium are used. These phenomena need further investigation.

COMMENT

The difference in mortality in the two series is highly significant as measured by the Chi square test. The clinical improvement impressed all observers that the potassium therapy enabled the babies to appear relatively well sooner than when the conventional therapy was used. The duration and intensity of the diarrhea was not apparently altered by the potassium administration.

Since the present study was finished, further trials with potassium chloride-sodium chloride-lactate have been carried out with equally successful results. It is felt that further study will show that parenteral therapy is not necessary after twenty-four hours, if the initial treatment has restored extracellular electrolyte and partially restored intracellular potassium. Recently the potassium chloride-sodium chloride-lactate solution has been given by mouth after the outlined treatment has been carried out for twenty-four hours; the solution is given in a mixture of equal parts of the potassium chloride-sodium chloride-lactate mixture, water, and 5 per cent solution of glucose. About 150 c.c. per kilogram of body weight is offered per day. The oral fluid is divided into suitable amounts to be ingested every three to four hours. This procedure apparently enables the patients to replace any further loss of electrolyte during the period of fasting, while the stools are still watery. One of the authors (D. C. D.) had tried to institute milk feedings fortified with potassium chloride at an earlier stage than is indicated by previous experience with the conventional type of treatment. The results were not such as to suggest that potassium therapy will permit milk feedings to be resumed at an earlier stage of the treatment than has been customary. In general, the potassium therapy does not apparently shorten the period of watery diarrhea, but it does enable the babies to withstand a severe or prolonged attack that would otherwise be fatal. One of the imponderable advantages of the treatment may have been that it has given the authors the courage and confidence in the final outcome which led to a sufficiently long period of fasting.

A dogmatic outline for the treatment of diarrhea is presented elsewhere.⁸ It is realized that further work is necessary to show the best way of giving potassium chloride, along with sodium chloride, and sodium lactate (or sodium bicarbonate). There can be no doubt that the treatment of the future will take into account the results presented in this and the previous paper,³ and that the mortality of infants suffering from the severe dehydration of diarrhea can be reduced to a much lower figure than has been the case in the last twenty years.

SUMMARY

A new plan for the treatment of diarrhea in infants is described. The various procedures which have been employed during the past twenty years are followed except that replenishment of body electrolyte is accomplished by adding potassium chloride to the solutions containing sodium chloride, sodium lactate, and glucose. In all severely ill patients, blood or plasma infusions are also carried out.

The results obtained with the new treatment in the last half of the diarrhea season are compared with the results obtained with the old treatment during the first half of the diarrhea season. The two series of cases were of comparable severity. With the new treatment 3 of 50 patients died; with the conventional treatment 17 of 53 patients died. The decrease in mortality was not accompanied by a shortening of the duration or a decrease in intensity of the diarrhea. Administration of potassium chloride in conjunction with the

other established procedures enables the babies to recover from some attacks of diarrhea that would otherwise be fatal.

Two complications of the new treatment were encountered: (1) Potassium intoxication with complete heart block developed once, but recovery followed treatment. (2) Five patients developed intense erythema followed by desquamation. While this complication did not otherwise alter the course, it is probably a consequence of the new treatment.

The precautions necessary for the prevention of potassium intoxication are briefly discussed.

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POTASSIUM INTOXICATION

REPORT OF AN INFANT SURVIVING A SERUM POTASSIUM LEVEL OF 12.27 MILLIMOLES PER LITER

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THE recent studies of Darrow¹ and Govan and Darrow² have demonstrated the value of potassium in the treatment of dehydration resulting from diarrhea. The therapeutic use of potassium is without danger provided the concentration of this ion in the extracellular fluid is not excessively elevated. Ringer and Murrell,³ and Howell⁴ were first to demonstrate the inhibitory effect of the potassium ion upon the heart. Winkler and associates⁵ have studied the electrocardiographic changes which occur in dogs as the concentration of potassium in the serum is gradually raised. Intraventricular block occurred when the concentration was a little more than doubled, and cardiac arrest occurred at levels of 14 to 16 mM per liter.

Smillie,⁶ in 1915, described potassium intoxication in patients receiving potassium therapy. He found that amounts of potassium which did not affect the normal individual produced severe effects in a patient with impaired renal function. Following this initial report, numerous cases of potassium poisoning have been described, yet no recovery has been recorded following elevation of the serum potassium to concentrations of more than 12 mM per liter.

REPORT OF A CASE

In September, 1945, a 12 day-old white girl (D. L. J., No. 43515) was admitted to the Harriet Lane Home because she had had watery diarrheal stools for two days prior to admission. The family history was noncontributory to the present illness. The birth was uncomplicated and spontaneous. The infant was exposed, in a nursery, to an epidemic of diarrhea of the newborn. At the age of 10 days the infant began to have greenish liquid stools. The following day the diarrhea became more severe and continued on the twelfth day, when she was brought to the Harriet Lane Home.

Physical Examination.—The physical examination revealed a dehydrated, emaciated but alert infant who was acutely ill. There was loss of skin turgor, depression of the anterior fontanel, and the eyes were sunken. The heart was normal in rate and rhythm, and no adventitious sounds were heard. The abdomen was flat and the liver edge was barely palpable. Neither the spleen nor the kidneys were felt. The genitals appeared normal. Scattered over the arms and legs was a splotchy red papular eruption. On the palms and soles were numerous large bullous impetiginous lesions.

Course.—The infant was isolated and during the first three days of hospitalization was given nothing by mouth. During this period the infant was given, intravenously and subcutaneously, 100 c.c. per kilogram of body weight of a solution having approximately the following composition:

K	35 mM per liter
Na	122 mM per liter
Cl	104 mM per liter
Lactate	53 mM per liter

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In addition, sufficient 5 per cent glucose solution was administered intravenously to bring the fluid intake to 200 c.c. per kilogram of body weight per day. Toward the end of the third hospital day the stools were normal and the general condition had improved. On the fourth hospital day a feeding mixture of equal parts of skimmed milk and lactic acid milk with 5 per cent dextrimaltose added was given. From this day until the ninth hospital day the caloric intake was gradually increased until the baby was receiving 60 calories per kilogram of body weight.

On the tenth hospital day the infant again began to have frequent large watery stools. Between 6 A.M. and 12 noon on the eleventh hospital day the baby had six large liquid stools and began to show evidence of dehydration despite a fluid intake of 175 c.c. of fluid per kilogram of body weight per day. The feeding was discontinued and 200 c.c. of the potassium chloride-sodium chloride-lactate solution were injected subcutaneously, without any preceding administration of salt solution.

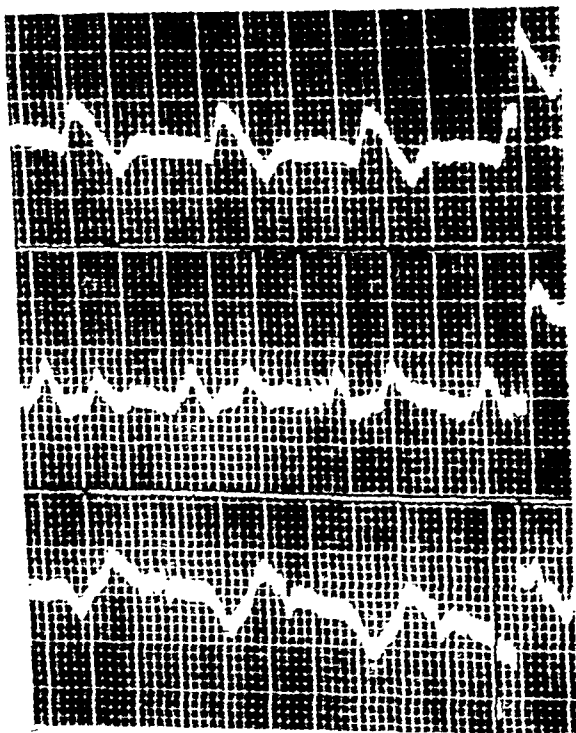


Fig. 1.

One hour later the baby appeared to be in shock. Examination revealed the skin to be a grayish color, she was listless and had a very feeble cry, the extremities were cold, and the heart rate was 80 per minute. An electrocardiogram (Fig. 1) taken at this time revealed evidence of first degree heart block, intraventricular block, pathological T waves in all leads, depression of the S-T segment, absence of the P waves in Lead I, and low voltage. These changes are typical of those described by Winkler, Hoff, and Smith⁵ as representing severe potassium intoxication. Blood was drawn at this time for a serum potassium determination. The condition of potassium poisoning was recognized on clinical grounds and the infant was promptly given 15 c.c. of calcium gluconate intravenously and 150 c.c. of hypertonic glucose solution. Within a few minutes she seemed to respond to this therapy. She was then given a transfusion of whole blood. One hour after therapy was started, a second electrocardiogram (Fig. 2) revealed partial recovery. The heart rate at this time had risen from 80 to 110 per minute. There was no evidence of intraventricular block and the T waves in Lead I were normal. Heart block was still evident and the

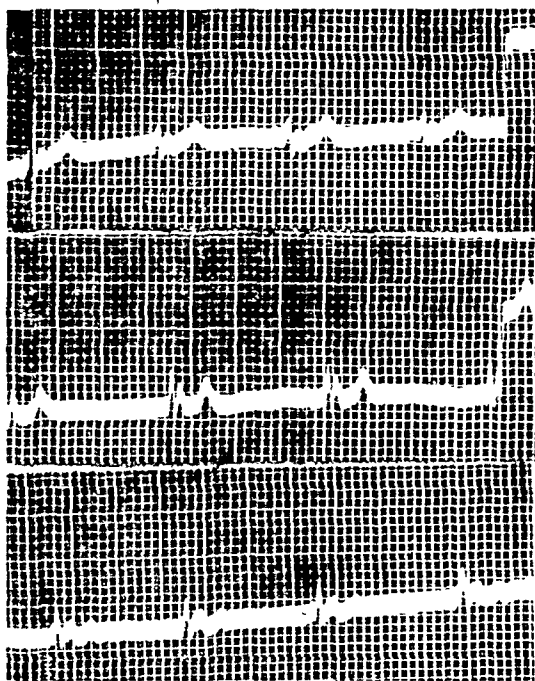


Fig. 2.

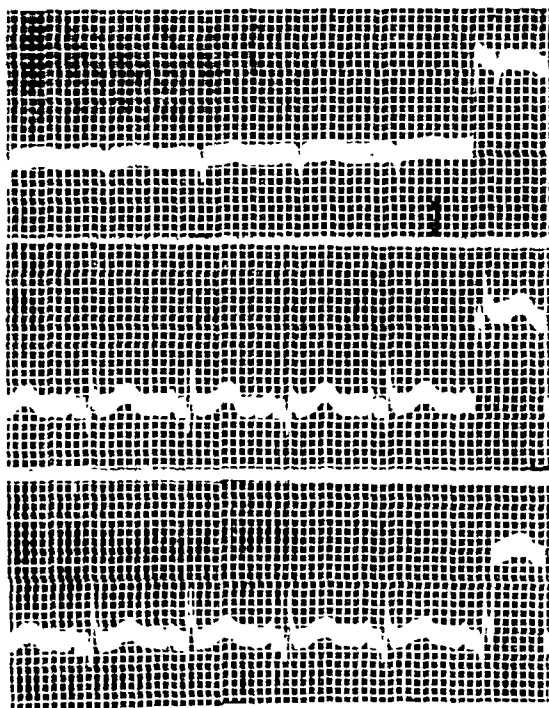


Fig. 3.

P waves were isoelectric in Leads I and II. Two hours after the initial therapy, a third electrocardiogram was taken. This showed complete recovery in Leads II and III. Technical difficulties were responsible for the effect seen in Lead I. The serum potassium level determined on the blood sample taken just prior to treatment proved to be 12.3 mM per liter. The infant continued to improve and was discharged two weeks later in good condition.

DISCUSSION

The potassium intoxication evident in this 3-kilogram infant was manifest one hour after a subcutaneous infusion of 200 c.c. of the potassium chloride-sodium chloride-lactate mixture. The amount of potassium (8 mM) administered, even if it had been absorbed immediately, was enough to raise the extracellular potassium concentration only 5 mM per liter. Yet, at the onset of the intoxication, the serum potassium level was 12.27 mM per liter. The potassium administered to the infant during the first diarrheal episode may have replaced any deficit of cellular potassium and allowed potassium to accumulate in the extracellular fluids. It is, therefore, possible that this infant was given an injection of potassium at a time when the concentration of potassium in the serum was already high. The oliguric state was also a contributing cause. The baby was known not to have voided for five hours before the parenteral potassium was administered.

The first signs of the intoxication were the onset of cyanosis and clinical signs of shock, which resulted from the slowed circulation secondary to the bradycardia and heart block. Improvement in the infant's color and an increase in the heart rate immediately followed the intravenous injections of calcium gluconate and hypertonic glucose solutions. Within one hour the infant was clinically asymptomatic, although minor changes in the electrocardiogram persisted. At the end of two hours the electrocardiogram was normal.

In treating this infant, the calcium ion was supplied to counteract the inhibitory effect of potassium upon the heart.⁵ The hypertonic glucose was given not only as a diuretic but also to enhance the deposition of glycogen in the liver. Fenn⁹ has demonstrated that when glycogen is deposited in the liver it is accompanied by potassium and water. It was thought that the injection of a hypertonic glucose solution would stimulate glycogen deposition in the liver and thus reduce the concentration of potassium in the extracellular fluids. This case demonstrates that prompt and specific therapy will relieve severe potassium intoxication.

SUMMARY

An infant suffering with potassium intoxication recovered following the intravenous injection of calcium gluconate and hypertonic glucose solutions.

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HOT BATHS IN THE TREATMENT OF EARLY INFANTILE PARALYSIS

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IMMERSION in warm water during the early phases of infantile paralysis has been used for some time and has been described by different authors for relief of soreness and muscle tightness,¹⁻⁴ but this approach has never been widely applied. Our results obtained so far with this method seem to us to justify the re-emphasis of this simple procedure.

We would like to do this with all the reserve necessarily needed for the recommendation of any treatment approach in infantile paralysis at the present time. The symptoms in this disease vary widely; spontaneous recoveries are frequent. The possible value of any treatment form can be determined only by the comparison of large groups of similar cases treated in different ways and uniformly recorded. We are lacking in sufficient numbers and necessary controls to draw valid conclusions; but we feel that the number of our patients is large enough to derive a clinical impression of the value of the treatment approach we are reporting.

We have treated all patients with infantile paralysis with Kenny packs in the 1941, 1942, and 1943 outbreaks. It was our impression that muscle soreness and stiffness responded more quickly in a large percentage of patients than with previously employed methods. Each year, however, a number of patients were observed in whom pain and stiffness remained in spite of long periods of packing. In November, 1943, we decided to treat several patients, who remained tender and very stiff in spite of prolonged packs, with frequent daily immersions in hot water. We observed a definite spurt in loosening up and decreased pain. Gradually we prescribed this treatment to an ever-increasing number of patients.

After January, 1944, hot baths became the treatment of choice and packs were prescribed only for those patients who for one reason or another could not be put into the pool; for instance, because of the patient having to wear a plaster boot, or because of incontinence. Until Sept. 1, 1945, we have treated 307 patients.

The technique we are using is as follows: Patients are put into water of a temperature of 104° F. The water is shallow so that the patient can lie flat with his head only very slightly raised on a headrest (Fig. 1). Gentle, free motion is not restricted but no exercises of any kind are given.

The lifting is done either on light canvas stretchers or by two to four persons according to the patient's height, leaving the patient's body straight to prevent pull on tender muscles (Fig. 2). Immersions are started as soon as the patient has been admitted—usually from an isolation hospital. For pa-

tients with marked stiffness and tenderness, we prescribed six immersions a day, lasting fifteen to twenty minutes each. As pain and stiffness subside, the number of immersions is gradually reduced. Bathing caps protect the hair from getting wet and ear plugs are inserted to protect the ears. At the end of each immersion, the patient is thoroughly dried and wrapped in wool blankets. Systemic reactions are carefully watched for during the first two weeks. Rectal temperature readings are taken following each immersion.



Fig. 1.

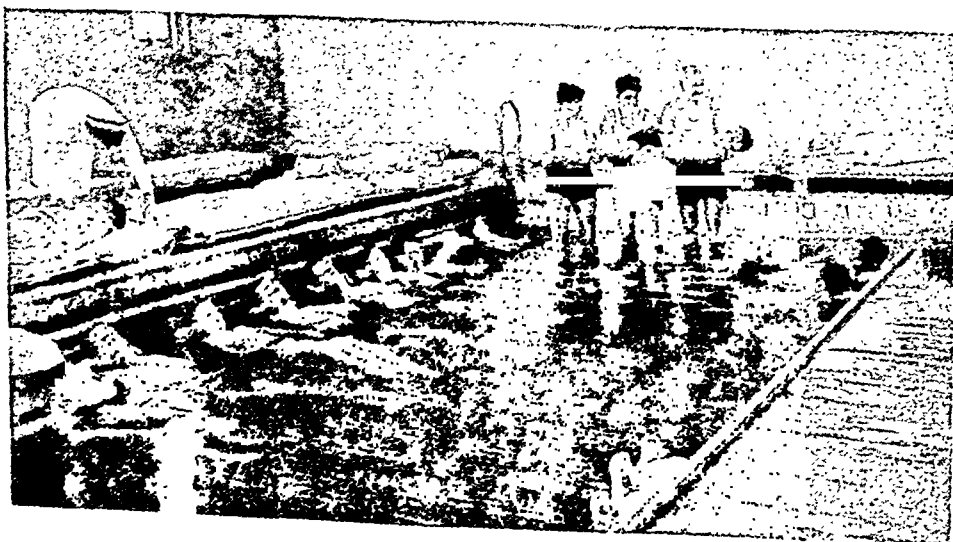


Fig. 2.

Blond, fair-skinned children may develop temperatures up to 101° F., but these will return to normal in all cases within an average of fifteen minutes. All patients receive from 2 to 8 Gm. of salt tablets daily according to their weight, and their fluid intake is forced.

Other treatment procedures such as re-educational or passive exercises are given during interval periods. If passive stretching is indicated, it is given immediately following the hot bath.

As we have been putting large numbers of patients into pools simultaneously, incontinence of feces or urine precluded this form of treatment for some. If individual baths could have been used, these patients also could have had immersions.



Fig. 3.—Case 1, J. T. Onset Aug. 14, 1943. Date of photograph Feb. 14, 1944.

Several patients developed colds while undergoing this treatment, but in looking over the case incidence and comparing it with the incidence of colds in other years during the same period, we found that the number of colds had not increased. Children with discharging or sensitive ears are protected with particular care from getting water into the auditory canals.

In order to get objective findings and to leave as little room as possible for subjective interpretations on the part of the individual examiner, we have tried to establish a routine of examination for our patients. Flexibility and muscle tightness are recorded in angles of motion and distance in inches. Tenderness and pain are recorded at rest, in response to pressure and to stretching, and graded as 0, \pm , 1+, to 4+. Muscles are tested regularly according to the Lovett system.



Fig. 4.—Case 1, J. T. Date of photograph March 31, 1944.



FIG. 5.—Case 1, J. T. Date of photograph March 31, 1944.

	PACKS STARTED DAYS AFTER ONSET	NUMBER OF DAYS CONTINUED	FLEXIBILITY	FLEXIBILITY BEFORE STARTING POOL TREAT- MENT	DAYS OF POOL TREATMENT				
					13	34	46	61	
Case 1, J. T. History no. 3151 Age: 5 years Sex: male Date of onset: Aug. 14, 1943	1	155	Head	Could be lifted 2 1/2"	Rigid	Slightly rigid	Free	Free	
			Trunk flexion: knees straight	130"	140°	100°	90°	90°	
			Forehead to knees: knees straight	23"	110°	13"	0"	0"	
			Forehead to knees: knees bent	18"	22°	5"	0"	0"	
			Shoulders	Pulled up, cupped	11°	+	0	0	
				++	+				
			Back	Held rigid	++	++	++	+	
				++					
			Straight leg raising: right	135°	110°	100°	100°	95°	
			left	125°	115°	105°	105°	95°	
			Hip flexion: right	90°	70°	50°	Free	Free	
			left	90°	70°	50°	Free	Free	
			Knee flexion: right	115°	95°	85°	90°	70°	
			left	110°	95°	90°	90°	70°	
			Ankle dorsiflexion: right	100°	95°	95°	85°	85°	
			left	105°	100°	100°	95°	95°	
			Pain to stretching	3+	2+	+	0	0	
			Pain to pressure	+	+	0	0	0	

Comment: Had prolonged intensive packs with only little improvement in stiffness, and continued marked pain; with hot pools he loosened up slowly but consistently (Figs. 3 to 5). (This is one of the original cases responsible for our starting hot pool therapy.)

	PACKS STARTED DAYS AFTER ONSET	NUMBER OF DAYS CONTINUED	FLEXIBILITY	FLEXIBILITY BEFORE STARTING POOL TREAT- MENT	DAYS OF POOL TREATMENT	
Case 2, C. S. History no. 3144 Age: 15 years Sex: female Date of onset: Sept. 9, 1943	4	103	Neck flexion	Free	17	
			Trunk flexion: knees straight	130°	Free	
			Forehead to knees: knees straight	25°	90°	
			Forehead to knees: knees bent	14°	9°	
			Back	Mild curve in lower dorsal and cervical spine	4°	0°
			Upper extremities	Free	Free	
			Straight leg raising: right	135°	Free	
			left	140°	90°	
			Knee flexion: right	30°	90°	
			left	30°	90°	
			Ankle dorsiflexion: right	83°	Free	
			left	103°	Free	
				not be tested—sprained ankle	Free	
				Normal	90°	
				Could not be tested—sprained ankle	103°	
Pain to stretching					0	
Pain to pressure					0	
Pain to loosening of tightness; started to loosen up immediately after hot pools were instituted.					0	

	PACKS STARTED DAYS AFTER ONSET	NUMBER OF DAYS CONTINUED	FLEXIBILITY	FLEXIBILITY BEFORE STARTING POOL TREAT- MENT	DAYS OF POOL TREATMENT			
					24	47	54	87
Case 3, B. P. History no. 3357 Age: 13½ years Sex: female Date of onset: Aug. 20, 1941	1	50	Neck flexion	Slightly stiff	Free	Free	Free	Free
			Trunk flexion: knees straight	125°	100°	100°	90°	90°
			Trunk flexion: knees bent	100°	90°	90°	80°	80°
			Forehead to knees: knees straight	35"	26"	14"	7½"	6"
			Forehead to knees: knees bent	34"	6"	0"	0"	0"
			Shoulder abduction: right	60°	70°	45°	55°	55°
			Shoulder abduction: left	70°	80°	80°	80°	90°
			Elbow flexion: right	30°	Free	Free	Free	Free
			Elbow flexion: left	35°	Free	Free	Free	Free
			Hip flexion: right	60°	Free	Free	Free	Free
			Hip flexion: left	70°	Free	Free	Free	Free
			Straight leg raising: right	130°	90°	90°	90°	90°
			Straight leg raising: left	125°	100°	90°	90°	90°
			Knee flexion: right	Free	Free	Free	Free	Free
			Knee flexion: left	Free	Free	Free	Free	Free
			Ankle dorsiflexion: right	90°	80°	80°	80°	80°
			Ankle dorsiflexion: left	90°	80°	80°	80°	80°
			Pain to stretching	4+	2+	0	0	0
			Pain to pressure	2+	0	0	0	0

	PACKS STARTED DAYS AFTER ONSET	NUMBER OF DAYS CONTINUED	FLEXIBILITY	FLEXIBILITY BEFORE STARTING POOL TREAT- MENT	DAYS OF POOL TREATMENT				
				12	36	50	69		
Case 4, A. G. History no. 3288 Age: 8 years Sex: male Date of onset: July 28, 1944	1	34	Trunk flexion: knees straight	165°	140°	120°	110°	90°	
			Trunk flexion: knees bent	95°	90°	90°	90°	90°	
			Forehead to knees: knees straight	30"	21"	19 1/2"	12"	5"	
			Forehead to knees: knees bent	19"	10"	6 1/2"	0"	0"	
			Shoulders	Right elevated	Right elevated	Right elevated	Right elevated	Slight elevation persisted	
			Back	Rt. up. dorsal curve	Rt. up. dorsal curve	Rt. up. dorsal curve	Rt. up. dorsal curve	Slight curve persisted	
			Hip flexion: right	60°	50°	30°	Free	Free	
			left	70°	60°	40°	Free	Free	
			Straight leg raising: right	130°	150°	130°	125°	90°	
			left	145°	140°	120°	120°	90°	
			Ankle dorsiflexion: right	90°	Free	Free	Free	Free	
			left	95°	95°	105°	Plaster	90°	
			Pain to stretching	3+	2+	0	0	0	
			Pain to pressure	3+	2+	0	0	0	

	PACKS STARTED DAYS AFTER ONSET	NUMBER OF DAYS CONTINUED	FLEXIBILITY	FLEXIBILITY BEFORE STARTING POOL TREAT- MENT	DAYS OF POOL TREATMENT				
Case 5, P. S. History no. 3327 Age: 9 years Sex: female Date of onset: Aug. 26, 1944	1	17	Trunk flexion: knees straight	165°	9	25	45	56	108
			Trunk flexion: knees bent	130°	160°	130°	100°	100°	90°
			Forehead to knees: knees straight	35"	100°	90°	85°	85°	85°
			Forehead to knees: knees bent	36"	33"	27"	21"	10"	0"
			Hip flexion: right	100°	29"	13"	4"	0"	0"
			left	95°	90°	70°	40°	20°	Free
			Straight leg raising: right	160°	90°	60°	30°	Free	Free
			left	165°	155°	140°	120°	105°	90°
			Knee flexion: right	85°	30°	Free	Free	Free	Free
			left	85°	35°	Free	Free	Free	Free
			Ankle dorsiflexion: right	120°	110°	110°	110°	105°	95°
			left	120°	110°	105°	95°	95°	95°
			Pain to stretching	4+	3+	1+	0	0	0
			Pain to pressure	4+	2+	0	0	0	0
			Was extremely tender; pain and stiffness subsided gradually						

	PACKS STARTED DAYS AFTER ONSET	NUMBER OF DAYS CONTINUED	FLEXIBILITY	FLEXIBILITY BEFORE STARTING POOL TREAT- MENT	DAYS OF POOL TREATMENT				
					8	14	28	56	
Case 6, B. A. History no. 3338 Age: 8½ years Sex: female Date of onset: Aug. 17, 1944	1	30	Neck flexion	Slightly stiff	Free	Free	Free	Free	
			Trunk flexion: knees straight	160°	130°	115°	105°	90°	
			Trunk flexion: knees bent	95°	90°	90°	85°	85°	
			Forehead to knees: knees straight	32"	25"	19"	12"	0"	
			Forehead to knees: knees bent	20½"	11"	0"	0"	0"	
			Hip flexion: right	Free	Free	Free	Free	Free	
			left	90°	40°	Free	Free	Free	
			Straight leg raising: right	160°	140°	120°	100°	90°	
			left	170°	135°	115°	100°	90°	
			Knee flexion: right	Free	Free	Free	Free	Free	
			left	30°	Free	Free	Free	Free	
			Ankle dorsiflexion: right	100°	95°	90°	90°	90°	
			left	105°	100°	100°	100°	100°	
			Pain to stretching	4+	2+	±	0	0	
			Pain to pressure	4+	2+	±	0	0	

Until Sept. 1, 1945, we have treated 35 patients with onset in 1943, 242 with onset in 1944, and 30 with onset in 1945.

All patients of the 1943 outbreak had prolonged periods of packs before they were put into hot water. This group is valuable because it allows us to compare the responses of the patient to packs and to baths. It was our impression, as stated before, that the immersions in hot water speeded up the process of relaxation and elimination of pain from stretching. The case reports illustrate this point.

COMMENT

In spite of having used the technique described for nearly two years, we are making this report only hesitantly and in the form of a preliminary one. We feel, however, that by now we have gained enough information to warrant this communication—especially in order that new victims of infantile paralysis might benefit by our experience.

If one considers, from a purely practical point of view, the relative ease with which baths or hot packs can be given, one will find that the application of hot baths is simpler, especially in patients' private homes or in institutions not especially equipped for the treatment of infantile paralysis. In order to give effective hot packs, four prerequisites are essential which, in our experience, are not often found simultaneously. These are:

1. Ability to determine exact location of so-called spasm
2. Good heating equipment for packs at bedside of patient
3. Correct technique in applying these packs
4. Two workers

Hot baths, on the other hand, will cover any area of muscle tightness regardless of exact location. The equipment consists of a bathtub of sufficient length so that the patient can lie in an extended position. It requires from two to four people to lift the patient in and out of the bath; therefore, the treatment can be given wherever there is a sufficiently long tub and enough help to lift the patient in and out.

In comparing our treatment results, it is our impression that hot baths relieve muscle soreness and tightness faster and more effectively than Kenny packs. Subjectively, the patients prefer the pool treatment, and nearly all of those who had both, and who were old enough to express an opinion, felt that their pain was relieved more rapidly by the baths.

We have adhered so far to one standard technique in order to get an impression with a sufficient number of patients. It is possible that the temperature of 104° is not the optimum one. We will have to try higher and lower temperatures. In view of the fact that mild fever therapy has been reported to be beneficial in relieving soreness and tightness,⁵ it may be that the element of raising the patient's temperature may be an important one. On the other hand, beneficial results have been reported using body temperature only.⁴ Whether the effect of mineral water is of importance will also have to be evaluated.

We have limited ourselves entirely to the discussion of the uses of hot baths in the treatment of muscle tightness and muscle soreness and have left entirely aside the use of pools in the treatment of the paralysis for ambulation and in re-education of coordinated function, as this is outside the scope of this report.

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THE USE OF NORMAL SERUM GAMMA GLOBULIN ANTIBODIES (HUMAN) CONCENTRATED (IMMUNE SERUM GLOBULIN) IN THE PREVENTION AND ATTENUATION OF MEASLES

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MEASLES in young infants and in debilitated children is often a very serious disease. Therefore, the procurement of either an active or passive prophylactic agent that is easily available, nontoxic on administration, and of uniformly high potency, is urgently needed. The agents heretofore used in passive prophylaxis: convalescent serum, pooled adult serum, normal adult blood, and placental immune globulin, are all deficient in one or more of these categories. Recently Cohn, Oncley, Strong, Hughes, and Armstrong¹ have, in their work on human plasma fractionation, developed a gamma globulin fraction that has been shown by Enders² to contain many of the humoral antibodies, and by Stokes, Maris, and Gellis;³ Ordman, Jennings, and Janeway;⁴ Greenberg, Frant, and Rutstein;⁵ and Janeway^{6, 7} to be highly effective in protecting susceptible children against measles when it is injected shortly after the child is exposed.

Our purpose in this paper is to detail our experiences with the use of this material, normal serum gamma globulin antibodies (human) concentrated (immune serum globulin), in the prevention and attenuation of measles during the past two years. The material used will hereafter be referred to as "gamma globulin."

MATERIAL

Between April 29, 1943, and Aug. 1, 1944, we have administered gamma globulin by intramuscular injection to 267 susceptible children within eight days after exposure to measles for the purpose of preventing or attenuating the disease. Of this group, 113 children were on the pediatric or orthopedic wards of the Gallinger Municipal Hospital, 37 were exposed in nursery schools, and 117 were intimately exposed at home to a sibling with measles.*

RESULTS

1. *Hospital Exposures.*—Measles was very prevalent in Washington in the spring of the years 1943 and 1944, and on fifteen occasions appeared on the pediatric or orthopedic wards of the Gallinger Municipal Hospital. All patients in the same or closely adjacent rooms were considered contacts with measles patients, and all patients treated or visited by one staff member with very early measles were considered contacts, provided the medical history showed that the

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The gamma globulin used in these studies was developed from blood collected by the American Red Cross and produced under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development, and Harvard University. Use of this material was authorized by the Naval Medical School, Bethesda, Md.

*A few of the children exposed at home and at school were treated by us or by the members of the pediatric staff of the Gallinger Municipal Hospital. The remainder were the private patients of Drs. William S. F. Burdick, Sander E. Lachman, Joseph S. Wall, John A. Washington, and of Washington, D. C., and of Dr. Robert C. Hood of Arlington, Va.

TABLE I. THE RESULTS OF A UNIFORM DOSE OF 2.0 C.C. OF GAMMA GLOBULIN IN PREVENTING MEASLES IN 113 CHILDREN EXPOSED ON THE HOSPITAL WARD

GROUP NO.	DAY AFTER EXPOSURE	NO. PATIENTS TREATED	PATIENTS FOLLOWED 21 DAYS OR MORE					PATIENTS FOLLOWED 10-21 DAYS IN HOSPITAL NO MEASLES	TOTAL NUMBER FOLLOWED			TOTAL NOT FOLLOWED
			TOTAL	IN HOSPITAL		IN CLINIC			NO MEASLES	MEASLES	TOTAL	
				NO MEASLES	MEASLES	NO MEASLES	MEASLES					
1	5	17	14	7	0	6	1*	1	14	1*	15	2
2	3	10	4	4	0	0	0	0	4	0	4	6
3	4	10	5	3	1*	1	0	2	6	1*	7	3
4	4	13	5	4	0	0	1*	2	6	1*	7	6
5	6	10	9	8	0	1	0	1	10	0	10	0
6	2	18	12	4	1†	7	0	2	13	1†	14	4
7	6	4	4	1	0	3	0	0	4	0	4	0
8	4	3	1	1	0	0	0	1	2	0	2	1
9	2	4	1	1	0	0	0	2	3	0	3	1
10	2	5	1	0	1†	0	0	3	3	1†	4	1
11	3	5	3	3	0	0	0	0	3	0	3	2
12	5	4	4	4	0	0	0	0	4	0	4	0
13	8	1	1	1	0	0	0	0	1	0	1	0
14	4	4	4	4	0	0	0	0	4	0	4	0
15	6	5	5	3	2*	0	0	0	3	2*	5	0
Total	2-8	113	73	48	5	18	2	14	80	7	87	26

*Modified measles.

†Patient developed measles four days after injection, six days after known exposure.

‡Patient developed measles three days after injection, five days after known exposure.

contact patient had not previously had measles. These patients ranged in age from 5 months to 10 years. Since we were desirous of protecting the wards as completely as possible against further measles, all susceptible contacts were given 2.0 c.c. of gamma globulin. The results are shown in Table I. There were fifty-three children who were observed on the wards for twenty-one days or longer. Of these, two developed measles within four days after receiving the gamma globulin, or six and five days, respectively, after the known exposure. Their measles was of average severity and they must be presumed to have had previous exposure and to have been treated more than eight days after exposure. Three other patients developed measles which was very mild and which apparently was attenuated by the globulin. There were twenty patients who were discharged before the lapse of twenty-one days but who were followed adequately in the outpatient clinic. Two developed mild, apparently modified measles, and eighteen did not. In addition, there were fourteen patients who were in the hospital for periods between ten and twenty days after exposure without developing measles. Our clinic follow-up was not complete, and we are uncertain whether they did or did not develop measles at home. However, they did not succumb while in the hospital and the other hospital patients were spared re-exposure. There were twenty-six patients who were discharged within ten days after exposure who were not followed in the outpatient clinic. Thus there were seventy-one patients who were given gamma globulin within eight days after exposure who were observed for twenty-one days or longer with only five cases of measles. Two of the patients who developed measles received globulin on the sixth day after exposure. In all the children the measles was attenuated.

2. *School Exposures.*—These patients are in three groups: In one nursery school there were ten children who were exposed to a patient in the early

catarrhal stage of measles. The exposed children were between 3 and 6 years of age. Five days after exposure each child received 1.0 c.c. of gamma globulin. None developed measles. However, one of these children was exposed at home to a sibling who became ill with measles five days after the school children had received globulin. This child developed a mild measles thirteen days after the second exposure and twenty-seven days after the first exposure. The school was re-exposed by this child. Three day later eleven children received 1.0 c.c. each of gamma globulin. There was no more measles in the school.

In the second group there were ten children between 3 and 5 years of age who played all day with a child with measles. Two days later eight children received 2.0 c.c. each and two children received 1.0 c.c. each of gamma globulin. None of the children developed measles. However, two of the children, aged 3 and 5, again were exposed to a sibling at home ten days after receiving gamma globulin. Both children developed a very mild measles twenty-five days after the first exposure and thirteen days after the home exposure. There were eight children who were re-exposed daily during the pre-eruptive stage of the illness of these boys, twenty-four to twenty-six days after they had received gamma globulin. None of the eight developed measles.

Finally there was a miscellaneous group of six children from 3 to 8 years of age who received 0.5 to 1.0 c.c. of gamma globulin four to eight days after school exposure. Two children, aged 4 and 3 years, who received 1.0 c.c. of gamma globulin each four and eight days after exposure, developed mild measles. Six children did not develop measles.

3. *Home Exposures.*—The experience with these patients is shown in Table II. The children varied in age from 4 months to 16 years. However, there were only six patients 8 years of age or over, only two were 12 years or over, and only one was under 5 months. All injections were given within eight days after exposure. Most of the patients received a dose of 0.5 to 1.0 c.c. that was, in most instances, calculated to modify rather than to prevent the disease. However, of eighty-three patients in this group, forty-eight (57.8 per cent) were completely protected and only four developed average measles. The high incidence of mild measles in the patients receiving between 1.0 and 2.0 c.c. of gamma globulin is undoubtedly accounted for by chance in a small group. Among twenty-three patients who received 2.0 c.c. or more, approximately 87 per cent were protected completely.

TABLE II. RELATION OF THE DOSE OF GAMMA GLOBULIN TO THE DEGREE OF PROTECTION IN 117 CHILDREN TREATED ON OR BEFORE THE EIGHTH DAY AFTER INTIMATE EXPOSURE TO MEASLES AT HOME

DOSE (C.C.)	AGE RANGE	TOTAL PATIENTS TREATED	NO MEASLES	MILD MEASLES	AVERAGE OR SEVERE MEASLES	COMPLICATIONS OF MEASLES
0.5 - 1.0	$\frac{1}{2}$ -11 yr.	83	48	31	4	1 Otitis media
1.25- 1.5	$\frac{1}{2}$ -10 yr.	11	4	7	0	0
2.0 - 3.0	$\frac{1}{2}$ -16 yr.	23	20	2	1	0
Total	$\frac{1}{2}$ -16 yr.	117	72	40	5	1 Otitis media

Re-Exposures.—There have been eight children in this group of 267 who have had intimate home exposure to siblings who developed measles from six to ten days after these eight patients were given gamma globulin. Five were protected from re-exposure, and three developed mild measles. They were as follows: Four children had received 2.0 c.c. of globulin; three were still protected and one developed mild measles from the second exposure. One child, aged 2, had been given 1.75 c.c. of gamma globulin. She was protected from both exposures. Two children had received 1.0 c.c. of gamma globulin. Both developed mild measles from the second exposure, and one child, aged 4, had been given only 0.5 c.c. of gamma globulin but was protected from the original exposure and from exposure to his mother who developed measles approximately one week after he had been immunized. And finally there were eight nursery school children, seven of whom had received 2.0 c.c. and one who had received 1.0 c.c. of gamma globulin, who were re-exposed twenty-four to twenty-six days later. None of them developed measles.

REACTIONS AND COMPLICATIONS

Reactions to the injections of concentrated gamma globulin were most noticeable by their absence. Only one child complained of slight local soreness for a short while, and in another 4-year-old child there was an unexplained subnormal temperature for two weeks. Nor were there any serious complications in the measles that followed the administration of gamma globulin. There were fifty-seven children who developed measles after being treated. In only one was there any complication, an otitis media in a 4-year-old boy who was given 1.0 c.c. of gamma globulin five days after exposure.

COMMENT

The group of patients who have been presented in this paper is too small for definite conclusions. However, certain trends are fairly evident. Gamma globulin, when administered intramuscularly, within seven or eight days after exposure to measles, is a potent prophylactic agent against this disease. While the uniform potency of different lots of the product has not been demonstrated, there is little likelihood of great variation as long as large pools of plasma are used in its manufacture. Nevertheless, exact calculation of the dosage to be employed for attenuation of or complete protection against measles will be very difficult. The age and size of the patient, the intimacy and duration of exposure before treatment, and the susceptibility of the individual patient are all variable factors that cannot be evaluated completely. Stokes, Maris, and Gellis³ recommend 0.02 c.c. per pound of body weight for attenuation and 0.08 c.c. per pound for protection. For children of five years and under the dosages are: 0.25 to 0.5 c.c. for attenuation and 2.0 to 2.5 c.c. for protection, and for children from 6 to 12 years 1.0 to 1.5 c.c. for attenuation and 4.0 to 5.0 c.c. for protection. We have shown that for the type of exposure found in nursery schools and kindergartens, 1.0 to 2.0 c.c. of gamma globulin is adequate for complete protection, and that in hospitals a uniform dose of 2.0 c.c. for children 10 years of age or less gives almost complete protection. With children exposed at home the results have

been more variable. There have been a few cases of severe measles, presumably in extremely susceptible individuals, even with large doses of globulin, and attenuation of measles has been somewhat uncertain.

Our results have shown a definite difference from those heretofore reported in this respect. When small doses were used by us, complete protection occurred in 58 per cent of the patients. This is extremely unusual, and cannot easily be accounted for. A considerable number of the children, injected and protected with 1.0 c.c. or less of gamma globulin, were treated by a single observer. It is possible that he failed to record some cases of very mild measles. However, since he used a lot of material not tested elsewhere or by other observers in our group in treating three-fourths of his patients, it is equally possible that he was using material of very high potency. Further observations are needed to evaluate this discrepancy.

SUMMARY

Gamma globulin was given to 267 exposed susceptible children in an effort to attenuate or prevent measles. Final results have been obtained for 241 children. Of these, fifty developed mild or attenuated measles and seven developed average measles. Among sixteen children who were re-exposed six to twenty-eight days after injection, the original treatment gave full protection to thirteen while three developed very mild measles. Only one child developed a complication (acute otitis media). There were no significant reactions to the injections of gamma globulin.

CONCLUSION

Normal serum gamma globulin antibodies (human) concentrated (immune serum globulin) is an effective, apparently nontoxic prophylactic agent for use in preventing or modifying measles.

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THE USE OF NORMAL SERUM GAMMA GLOBULIN ANTIBODIES (HUMAN) CONCENTRATED (IMMUNE SERUM GLOBULIN) IN THE TREATMENT OF PREMATURE INFANTS

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THE prevention of infection constitutes one of the most serious problems associated with the care of prematurely born infants. These infants have few if any humoral antibodies except the small amounts that normally pass the placenta. Consequently, if human antibodies could be made available in concentrated form, they might provide a valuable adjunct to the treatment of such infants. Cohn, Oncley, Strong, Hughes, and Armstrong,¹ in the course of their work on human plasma fractionation, have developed a gamma globulin fraction that was found by Enders² to contain a large number of humoral antibodies and was found by a number of other investigators³⁻⁷ to be highly potent agent in the prophylaxis of measles. The question of the possible value of this gamma globulin fraction as a general prophylactic against infection in a nursery for premature infants immediately arose. In an attempt to shed light upon this possibility, we gave gamma globulin to alternate infants who were admitted to the nursery for premature infants in the Gallinger Municipal Hospital from Jan. 1 to Dec. 31, 1944.

The purpose of the present paper is to present a summary of our findings in this study.

PROCEDURE

The material used as a possible prophylactic agent was normal serum gamma globulin antibodies (human) concentrated (immune serum globulin), hereafter called "gamma globulin." The patients treated were prematurely born infants who were admitted to the nursery for premature infants in the obstetric division of the Gallinger Municipal Hospital. In order to obtain a group of viable patients for study, the infants were admitted to the series when they were 24 hours old, thus eliminating infants who were dead or moribund at the end of the first day. Furthermore, all infants who were found on admission, or at any subsequent date, to be suffering from a congenital defect or disease incompatible with normal physical development were excluded from the series, as were a small number of infants whose names were inadvertently omitted from the list. All other infants were included in the study. Alternate infants were given 2.5 c.c. of gamma globulin by intramuscular injections on the second, eighth and

From the Department of Pediatrics, Gallinger Municipal Hospital, Washington, D. C.
The gamma globulin used in these studies was developed from blood collected by the American Red Cross and produced under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development, and Harvard University. Use of this material was authorized by the Naval Medical School, Bethesda, Md.

Lieutenants McMain and Antell made their contribution to this paper before entering the Army of the United States.

fifteenth days of life, and every two weeks thereafter until the infant reached a weight of 5 pounds and 8 ounces. This dose, at each injection, corresponded to the gamma globulin from 62.5 c.c. of normal pooled human plasma. The remaining infants received no globulin. The normal diet and the nursing care of the two groups of infants were the same, as was the treatment of sick infants after an illness became manifest.

It must be noted that this study was carried on at a time when, due to war-time shortages, the nursing staff in the nursery was greatly depleted. In consequence, the nursing technique was grossly inadequate, infection was frequent, and the over-all mortality was high.

RESULTS

There were 117 infants who received injections of gamma globulin and 113 who served as controls. The distribution of the two groups of infants according to birth weight, and the gross mortality encountered in each group and in each weight division are shown in Table I. The groups were highly comparable in weight distribution. There was no significant difference in mortality in the two groups, nor any sustained difference in weight in the two groups.

TABLE I. COMPARISON OF BIRTH WEIGHT AND MORTALITY IN PREMATURELY BORN INFANTS WHO DID AND WHO DID NOT RECEIVE INJECTIONS OF GAMMA GLOBULIN

BIRTH WEIGHT*	TOTAL		INFANTS RECEIVED GAMMA GLOBULIN		INFANTS RECEIVED NO GAMMA GLOBULIN	
	NO. OF INFANTS	INFANTS DIED	TOTAL INFANTS	INFANTS DIED	TOTAL INFANTS	INFANTS DIED
2.0 to 2.15 $\frac{3}{4}$	9	8	5	4	4	4
3.0 to 3.7 $\frac{3}{4}$	17	11	7	5	10	6
3.8 to 3.15 $\frac{3}{4}$	25	13	13	8	12	5
4.0 to 4.7 $\frac{3}{4}$	34	7	18	3	16	4
4.8 to 4.15 $\frac{3}{4}$	56	10	26	7	30	3
5.0 to 5.7 $\frac{3}{4}$	89	6	48	2	41	4
Total	230	55	117	29	113	26

*Weight expressed in pounds and ounces.

The morbidity rates for the infants who survived and were discharged from the hospital in good condition are shown in Table II. Since the number of patients is small, all types of illness are grouped together. The high incidence

TABLE II. COMPARISON OF BIRTH WEIGHT AND MORBIDITY IN PREMATURELY BORN INFANTS WHO LIVED, WHO DID AND WHO DID NOT RECEIVE INJECTIONS OF GAMMA GLOBULIN

BIRTH WEIGHT*	TOTAL INFANTS		INFANTS RECEIVED GAMMA GLOBULIN		INFANTS RECEIVED NO GAMMA GLOBULIN	
	NO. OF INFANTS	INFANTS ILL	NO. OF INFANTS	INFANTS ILL	NO. OF INFANTS	INFANTS ILL
2.0 to 2.15 $\frac{3}{4}$	1	1	1	1	0	0
3.0 to 3.7 $\frac{3}{4}$	6	6	2	2	4	4
3.8 to 3.15 $\frac{3}{4}$	12	11	5	4	7	7
4.0 to 4.7 $\frac{3}{4}$	27	21	15	11	12	10
4.8 to 4.15 $\frac{3}{4}$	46	38	19	16	27	22
5.0 to 5.7 $\frac{3}{4}$	83	65	46	36	37	29
Total	175	142	88	70	87	72

*Weight expressed in pounds and ounces.

of illness is accounted for in large measure by the grossly inadequate nursery personnel, and in part by the fact that any deviation from the normal, particularly with regard to gastrointestinal symptoms, respiratory tract symptoms, or general loss of vigor, was considered an evidence of illness. When judged by these standards, there was no appreciable difference in morbidity between infants who were given injections of gamma globulin and those who did not receive the preparation.

The gain in weight was studied as another possible criterion for the value of gamma globulin in the care of premature infants, with the average time to regain the birth weight and the average time to succeed to the normal discharge weight of 5½ pounds being the most objective figures available. The details of this comparison between the two groups of infants under study are shown in Table III. The average time required to reach each goal was slightly less in infants who were treated with gamma globulin, but the differences are so slight that they cannot be regarded as significant.

TABLE III. COMPARISON OF BIRTH WEIGHT, TIME TO REGAIN BIRTH WEIGHT, AND TIME TO GAIN DISCHARGE WEIGHT* IN PREMATURELY BORN INFANTS WHO SURVIVED, WHO DID AND WHO DID NOT RECEIVE INJECTIONS OF GAMMA GLOBULIN

BIRTH WEIGHT†	INFANTS RECEIVED GAMMA GLOBULIN			INFANTS RECEIVED NO GAMMA GLOBULIN		
	NO.	AVG. DAYS TO REGAIN B.W.	AVG. DAYS TO GAIN DISCH. WT.	NO.	AVG. DAYS TO REGAIN B.W.	AVG. DAYS TO GAIN DISCH. WT.
2.0 to 2.15½	1	43	82	0	—	—
3.0 to 3.7½	2	34	99	4	40	99
3.8 to 3.15½	5	32	75	7	27	74
4.0 to 4.7½	15	26	52	12	29	60
4.8 to 4.15½	19	25	45	27	26	44
5.0 to 5.7½	46	25	31	37	29	36
Total	88	26.1	42.1	87	28.4	49.5

*Discharge weight 5 pounds, 8 ounces.

†Weight expressed in pounds and ounces.

SUMMARY AND CONCLUSIONS

Gamma globulin, in doses of 2.5 c.c. (equivalent to the gamma globulin from 62.5 c.c. of normal pooled human plasma) given on the second, eighth, and fifteenth days of life and thereafter every two weeks until a discharge weight of 5 pounds, 8 ounces was reached, was given to 117 prematurely born infants; 113 infants of similar birth weight who received no gamma globulin were studied as control patients. There was no difference in the gross mortality and morbidity rates of the two groups of infants. Likewise, there was no significant difference in the time required for the two groups of infants to regain the birth weight or to attain a discharge weight of 5 pounds and 8 ounces.

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HEMOLYSIS FROM IRREGULAR ISOAGGLUTININS (COLD AGGLUTININS) FOLLOWING TREATMENT FOR ERYTHROBLASTOSIS FETALIS

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REPORTS of erythroblastosis fetalis, or hemolytic disease of the newborn, have become of such frequency in the recent medical literature that only those which show deviation from the usual course of the disease are worthy of attention. Our reason for this report of an infant suffering from this condition, is that recovery was complicated by the occurrence of cold agglutinins in its blood, that necessitated twenty-two transfusions over a period of three weeks, before recovery was complete.

CASE HISTORY

A female infant, weighing 6 pounds, 11 ounces, was born in the Presbyterian Hospital of a para i mother, following an eight-hour normal labor. The older sister had no abnormal conditions existing at birth or after, and was now $5\frac{1}{2}$ years of age and well. The infant was pale and listless at birth, with a spleen enlarged about one fingerbreadth below the costal margin. Blood examination showed the hemoglobin to be 60 per cent, 3,500,000 red cells, and 24,800 white cells. There were 22 per cent nucleated red cells, both normoblasts and erythroblasts, and 10 per cent myelocytes among the white cells. The infant's blood was Group A, subgroup A₁, Rh positive; the father's blood was Group A₁, Rh positive, and the mother's blood was Group A₁B, Rh negative. The diagnosis of erythroblastosis fetalis was made. We were unable to demonstrate anti-Rh agglutinins in the mother's blood until two weeks after delivery. They were still demonstrable after a year.

Treatment by transfusions was begun within three hours after birth with the results shown in Charts I to III (c.a. standing for cold agglutinins). During the first fifteen days of life, sixteen transfusions were given from the blood of five donors. Four of these donors were A₁, Rh positive, and one donor was A₁, Rh negative. None of these donors' blood agglutinated the blood of the infant or was agglutinated after incubation at 37° C. for one hour, which we have always assumed to be sufficient in these instances. While the infant's blood was very slightly improved, and the nucleated red cell count fell to 7 per cent, it was impossible to raise it to a satisfactory level. From the increasing icterus, urobilin, and blood cells in the urine, it was obvious that an intense hemolysis was taking place. The icterus index rose to 470 by the ninth day of life, and remained at that level until the sixteenth day of life. During this period the infant took feedings of pooled breast milk well and, except for the intense jaundice, was in fairly good condition.

It was then found that the infant's blood contained irregular isoagglutinins for each of these five donors, that clumped these donors' cells at 0° C., but did not clump the same cells at 20 or 30° C. Two A₁, Rh positive donors were obtained whose blood was not agglutinated by the infant's blood at 0° C. in vitro, and transfusions were given from this blood on the sixteenth day of life. Improvement was immediate. The blood rose to normal levels, the jaundice disappeared within twelve days, and the urobilin and blood cells disappeared from the urine. The nucleated red cells disappeared from the peripheral circulation and reticulocytes began to appear. After receiving twenty-two transfusions, or a total of 2,300 c.c. of blood, the infant was discharged on the thirty-third day of life. The chart shows the condition of the blood through the fifty-eighth day of life. The child is now $3\frac{1}{2}$ years of age and in good health.

*Our laboratory's results of the blood types, Rh factors, and agglutinins were checked by Israel Davidsohn, M.D., of Mount Sinai Hospital, Chicago, whom we wish to thank.

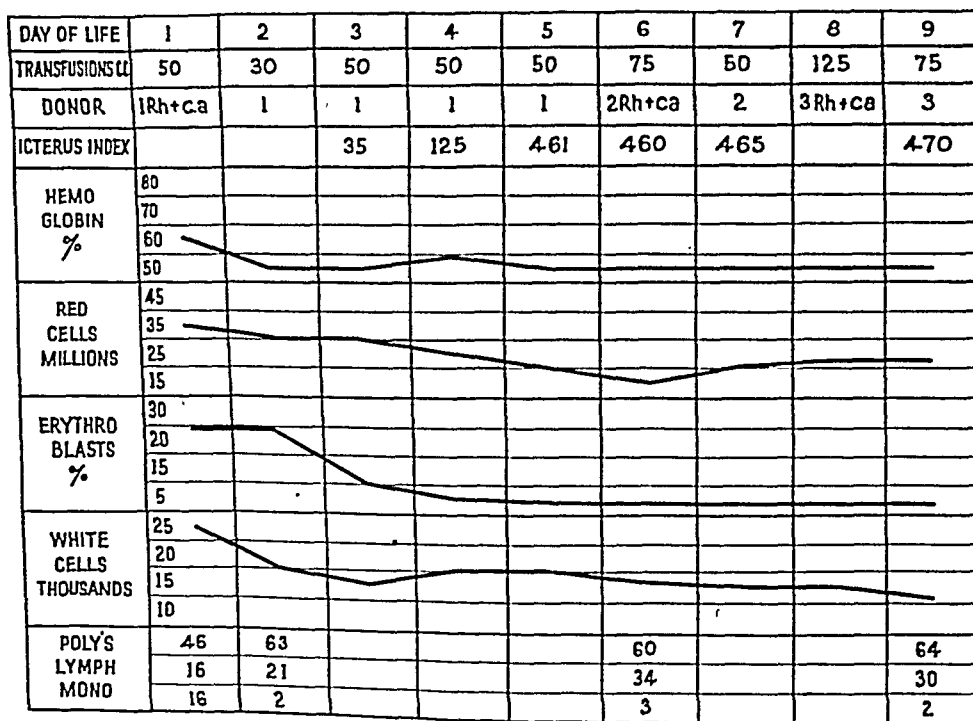


Chart I.

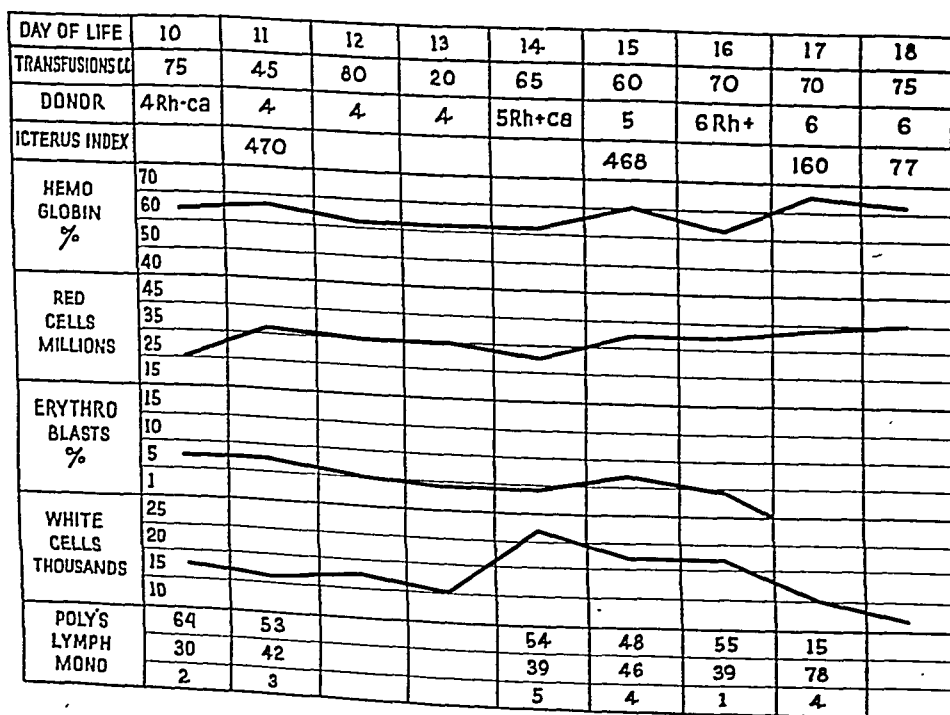


Chart II.

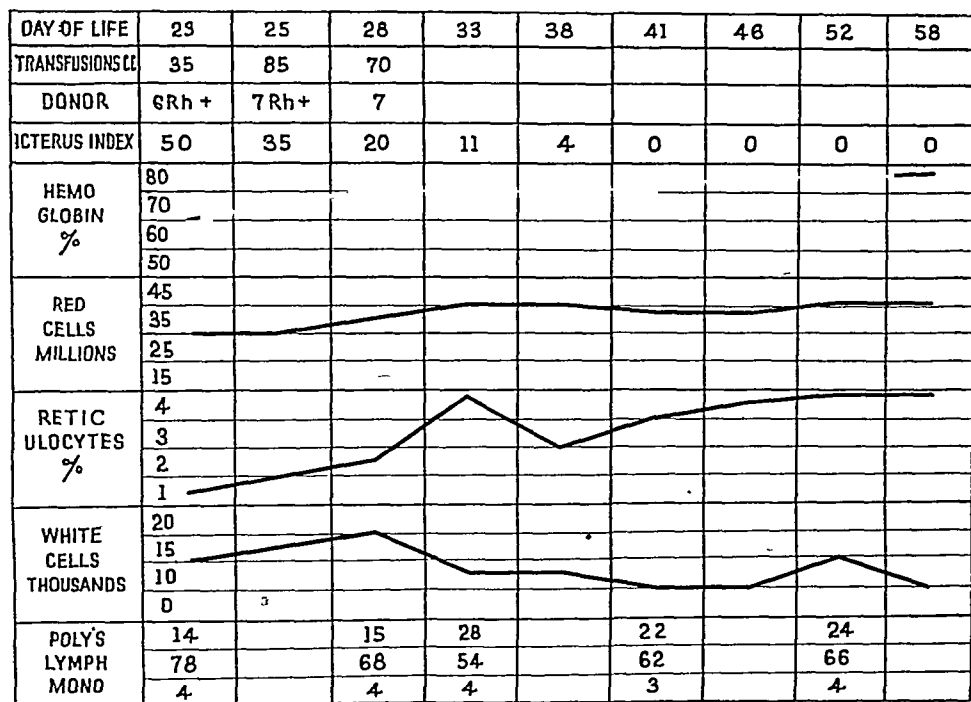


Chart III.

DISCUSSION

Inasmuch as the blood of both donor and recipient was of the same group, we were unable to demonstrate by the usual agglutination tests whether the blood of donor or recipient was hemolyzed. However, we feel that the hemolysis that occurred must have been entirely of the donor's blood, inasmuch as the recipient's blood contained the isoagglutinin, and the hemolysis ceased as soon as blood was found with which these irregular cold agglutinins did not react. This is also indicated by the fact that the red cells and hemoglobin of the infant did not appreciably fall much below their original level, and the amount of blood added by transfusions did not perceptibly increase the red cells or hemoglobin.

At first glance, a simple explanation of this experience would be that, in using the Rh-positive donors, all of the anti-Rh agglutinins that were circulating in the baby's blood, or were held by blocking antibodies, were used and recovery occurred when this was accomplished with the aid of the Rh-positive blood given after this time. When the anti-Rh agglutinins had all been used by the transfused Rh-positive blood, it would, of course, make no difference what kind of blood was then given in reference to the Rh factor. However, three Rh-positive donors were used over a period of the first week, then a change was made to an Rh-negative donor. This blood likewise resulted in the same destruction or hemolysis as shown by the failure of the red cells to increase, the continued high icterus index, and the urobilinuria. It has been known for a long time that in the treatment of these infants certain blood does not give uniformly

good results, and the hemolytic process continues. In such instances a change of donor is often beneficial. The explanation now given is that this blood was probably Rh negative, accidentally given, for formerly we were not aware of the Rh factor.

Our laboratory had reported that all of the blood given thus far was hemolyzed by the cold agglutinins existing in the infant's blood, but we had not considered that these could be a possible reason for the continued hemolysis. Inasmuch as no other factor could be found, we were about to change to type O blood when it was found that the blood of our sixth prospective donor was not hemolyzed by these cold agglutinins. When the blood was given the infant, the results were immediate as will be seen on the chart. We feel, therefore, that the Rh factor was not a part of the later hemolysis, although it was the original cause of the condition that existed at the birth of the child.

In this instance, therefore, we have a Group A₁ recipient whose blood carried isoagglutinins that clumped the cells of five Group A₁ donors at 0° C., but did not clump the same cells at 20 or 30° C. in vitro. This was in no way due to the Rh factor, because while the recipient was Rh positive, and suffered from transmitted anti-Rh isoantibodies from her Rh-negative mother, one of these donors was Rh negative and his blood was agglutinated as consistently as that of the other four Rh-positive donors. Recovery did not occur until the child was transfused with the blood of two other Group A₁, Rh-positive donors, whose blood was not agglutinated by the recipient's cold agglutinins.

As Landsteiner and Levine first pointed out, the irregular isoagglutinins in normal human sera are of four varieties: (1) those reacting with blood of subgroups A₁ and A₁B, found among individuals of subgroup A₂ and A₂B; (2) agglutinins reacting with all Group O blood, and less intensely with Group A₂; (3) all P negative individuals; and (4) unclassified, irregular isoagglutinins. The infant does not seem to fit any of the first three groups, nor have we been able to find any reference in the literature to hemolysis or agglutination occurring among Group A₁ individuals only. For this reason we have been unable to find any satisfactory explanation for this phenomena and simply report it as such. There is no other recourse except to place it in Group 4, as an irregular, unclassified isoagglutinin, contained in the blood of an A₁, Rh-positive recipient, which hemolyzed certain (five) A₁, Rh-negative and positive donors.

It has been stated that in general, immune isoantibodies are of greater significance in the severity of hemolytic transfusion reactions than natural isoantibodies. While there is a rough correlation between the titer of the isoantibodies in the in vitro tests and the severity of the reaction, serious hemolytic reactions have occurred in the absence of demonstrable isoantibodies. It would appear, as in this infant, that other properties of the isoantibodies are of greater significance than their behavior in vitro with respect to temperature. In this instance we have a severe hemolytic reaction resulting from isoantibodies in the recipient serum which have the properties of "cold agglutinins," instead of the usual hemolytic reaction, in which the antibodies behaved like "warm agglutinins."

The results of this series of transfusions show that in this type of newborn infants at least, factors other than the Rh isoagglutinins must be considered. As we have stated before, it is always well to give these infants a change of donors, even if they are group compatible, because of such irregular isoagglutinins as found in this instance.

In this respect we would like to point out again that this hemolysis caused the bilirubin to pile up in the blood stream and spill over into the tissues to such an extent that the child carried an icterus index of 470 for eleven days. This did not cause kernicterus or harm the child in any way. It has been mentioned so frequently in the recent literature, that kernicterus follows the hemolysis of blood given to these infants, or the hemolysis of the infant's blood if Rh-positive blood is given. We have not found kernicterus to be a frequent complication of this condition and do not believe that it is a necessary sequel to erythroblastosis neonatorum. The majority of reported instances show it to be associated with liver damage. We believe that the results of this case show the fallacy of the argument that any damage can be done the child by injections of either Rh-positive or Rh-negative blood.

CONCLUSIONS

An infant suffering from erythroblastosis neonatorum received transfusions from five donors of the same blood group, both of Rh-negative and Rh-positive blood. An intense hemolysis resulted from cold agglutinins in the infant's blood which reacted on the blood of these five donors. Recovery took place immediately after the blood from two Rh-positive donors was given that was not hemolyzed by the infant's cold agglutinins.

The infant completely recovered after receiving twenty-two transfusions, or a total of 2,300 c.c. of blood, over a period of thirty-three days. During this period the infant's icterus index rose to 470 and remained at this point for eleven days. This did not cause kernicterus, or harm the child in any way.

952 NORTH MICHIGAN AVENUE
104 SOUTH MICHIGAN AVENUE

A CASE OF STEVENS-JOHNSON DISEASE (ERYTHEMA MULTIFORME BULLOSA) TREATED WITH PENICILLIN

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THE case to be described is one of erythema multiforme bullosa, with severe mucous membrane lesions, which was treated with penicillin. We are reporting this case because we hope to point the way toward a method of treatment which will avoid eye complications in cases of erythema multiforme usually classified, because of their severity, as Stevens-Johnson disease.

This disease entity, according to Klauder¹⁷ and Lever⁴ in the United States, and many original sources elsewhere, is supposedly the erythema multiforme bullosa originally described by von Hebra³⁰ in 1860 and von Hebra and Kaposi³¹ in 1874, with the addition of severe involvement of the oral and other mucous membranes. However, the complete entity was classified as a separate disease by Rendu²⁷ in 1916, and by Feissinger and Rendu²⁸ in 1917, who believed they were dealing with a disease not previously recognized, which they called "Ectodermosa Erosiva Pleuri-orificialis." Stevens-Johnson disease,⁹ as reported in 1922, is then, only a very severe form of this condition, in which a certain proportion of patients develop eye sequelae as the most common complication.

Stevens-Johnson syndrome, as described, is a triad of skin, eye, and mucous membrane lesions, associated with marked general toxicity. The striking feature of this disease is an acute febrile condition, which occurs most commonly during spring and fall, usually in young males. Typically, there is an abrupt onset of fever, malaise, headache, and general toxicity. Simultaneously, or within twenty-four or seventy-two hours, there appears a crop of erythematous, multiform, sometimes irislike lesions on the upper and lower extremities, and to a lesser extent, on the body and even the face. These may be macules, vesicles, or pustules.

Usually about this time there is soreness of the oral mucous membrane, and vesicles appear on the buccal mucosa which eventually become membranous lesions producing a severe stomatitis. Likewise, similar lesions appear on the other exposed mucosae, and membranes may form on the anus, as well as on the mucosa of the meatus of the penis, or on the vaginal mucosa. The child is usually prostrate. However, the most striking and serious feature of this disease is a severe conjunctivitis which invariably develops in the Stevens-Johnson syndrome. These lesions present the serious threat to the patient, whereas the remainder of the syndrome subsides completely within from three to eight weeks. The conjunctivitis in typical cases, however, in the presulfonamide days caused partial or total blindness in seven of nine cases.⁹ In our tabulation of twenty-one cases

From the Service of Dr. Harry S. Altman, Department of Pediatrics, Lincoln Hospital.
This case was presented before the Pediatrics section of the New York Academy of Medicine Feb. 8, 1945.

of varying severity, only five patients received adequate doses of sulfonamide. These five recovered their sight; while seven patients, the most severe cases of the remaining sixteen (that is, those that were typical Stevens-Johnson disease), were left with total or partial blindness. Ophthalmic complications in erythema multiforme were first described by Fuchs²⁹ in 1876. Koke,⁷ in 1941, has referred to eighteen cases, of varying intensity, untreated by chemotherapy, fourteen of which resulted in total or partial blindness. Duke-Elder²³ classifies three types of eye lesions in erythema multiforme: (1) the catarrhal, (2) the purulent, and (3) the pseudomembranous. The last two usually lead to permanent eye damage.



Fig. 1.—Photograph taken day of onset of local penicillin therapy. Photophobia is present along with purulent ophthalmic discharge. Mouth shows ulceration and crusting of tongue and buccal mucosa.

We present this case, treated vigorously with sulfonamide and penicillin, locally and systemically, in the hope that subsequent cases will be treated by one of these methods, whichever proves more efficient. We therefore hope to eliminate the specter of blindness and debilitating eye sequelae from this disease syndrome.

Whatever the cause of this condition, local or systemic, allergic, anaphylactic, toxic or bacterial, there is no doubt that the tissues of the eye are invaded

by many pyogenic organisms which can be checked by local and/or systemic antibacterial agents. Of the twenty-one cases we tabulated from the literature, sixteen patients had eye cultures, of which nine showed *Staphylococcus aureus* in pure form, six showed mixed cultures of staphylococcus and streptococcus, and only one was sterile.

REPORT OF CASE:

R. M., a 9 year old white male of Czechoslovakian ancestry, born in the United States, was admitted to the hospital on Sept. 18, 1944, with a history of toothache two weeks before admission.



Fig. 2.—Left eye closed and puffy. Right eye, forcibly opened, shows injected vessels and inflammation of the conjunctiva with a glairy purulent discharge. Eyelashes are pasted together.

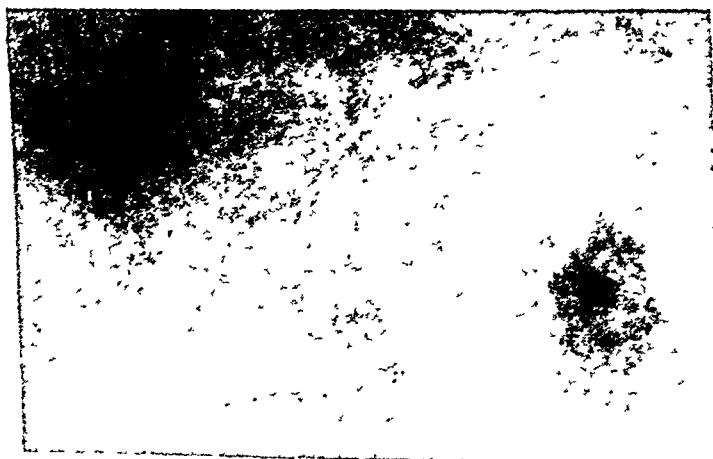


Fig. 3—Close-up of erythematous, bullous, punched-out, irislike lesion to the right of normal umbilicus (for comparison as to size).

One week before admission, the patient went swimming in a chlorinated, salt-water pool and the toothache returned. The patient was treated by local application to the gum and was relieved. That night "sores" appeared inside the mouth. A few hours before, the patient had felt weak and listless. His eyes became red and swollen. He developed photophobia. No rash was present. There was no itching. No drugs were given except an antipyretic after the onset of the systemic symptoms. There was no history of allergy or parasitic

infection. No rash was noted until one week after onset, when, because of the progression of the symptoms, he was admitted to Lincoln Hospital.

Past and family history was negative, except for familial history of rheumatic fever.

For three days before admission the patient had marked dysphagia and came to the hospital primarily because of dysphagia, photophobia, general malaise, and toxicity.

Physical Examination.—Temperature 101° F.; pulse, 120; respiration, 32; blood pressure, 110/75; weight, 59 pounds. The patient was a well-developed, well-nourished, 9-year-old white male, acutely ill, lying quietly in bed, producing large quantities of blood-tinged mucoid sputum. He was extremely toxic and without the strength to stand alone.

Skin: There were many 0.5 to 1.5 cm., round or oval, dark red, nonelevated, irishlike lesions. These were mostly located on the arms and legs and also on the trunk and face. A few had small vesicles in the centers, some had already crusted over (Figs. 3, 4, and 6).

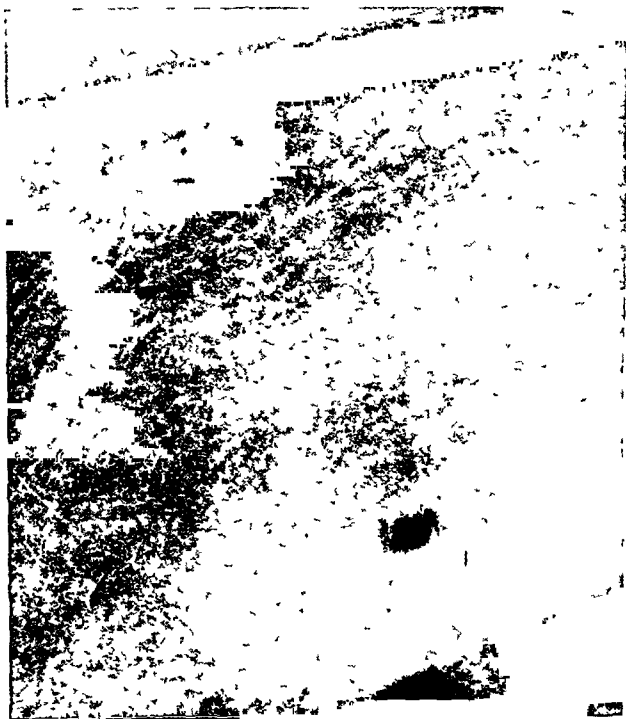


Fig. 4.—The erythematous punched-out lesions of hairy surface of arm in close-up.

Lymphatics: Several enlarged and tender anterior cervical lymph nodes.

Head: Symmetrical.

Ears: Negative.

Eyes: Eyes were held closed. The lids were swollen; there was marked chemosis and photophobia. The sclera and conjunctivae were deeply injected, with marked exudation of pus (Figs. 1, 2, and 5).

Mouth and Throat: There were bloody and dirty-gray, raised, membranous, and ulcerative lesions on the lips, buccal mucosa, margins of the tongue, and floor of the mouth. The gingivae were not affected. The membranes could be rubbed off, leaving a bleeding surface. There was extreme oral pain and tenderness. The lips had bloody encrustations and were edematous and puckered. The patient had sealorrhea, and the mouth was filled with blood-tinged mucus. The palate and uvula had small petechial hemorrhages (Figs. 1 and 5).

Nose: There was a purulent discharge from the nose. No membranes were seen.

Neck: Flaccid. No masses. Trachea in midline.

Chest: Heart negative. Lungs clear to percussion and auscultation.

Abdomen: Liver, spleen, and masses not palpable.

Extremities: Negative, except for skin.

Neurological Examination: Negative.

Rectum and Genitalia: Normal on admission. It may be noted that two days after admission, the child had not voided for twenty-four hours. It was then seen that there was an occlusive grayish membrane over the penile meatus. There was a similar membrane over the anal orifice. Both membranes were attached to the mucosa but could be removed by friction.



Fig. 5.—Crusting of lips over ulcerations. Typical facies.

Laboratory Examination.—(1) An admission eye smear showed many polymorphonuclears with large clusters of gram-positive cocci, and no intracellular organisms. A smear of the buccal mucosa showed many polymorphonuclears with many short chains of gram-positive cocci. Culture of the eyes and mouth revealed *Staph. aureus*. (2) Repeated urinalyses were negative throughout hospital stay. (3) Blood count (September 18) showed 13,600 white blood cells, and 94 per cent (13.2 Gm.) hemoglobin. Differential count revealed eosinophiles, 15; stabs, 1; polymorphonuclears, 51; basophiles, 1; monocytes, 5; and lymphocytes, 27. One week after admission the count showed 11,900 white blood cells; eosinophiles, 14; polymorphonuclears, 52; stabs, 4; and lymphocytes, 30. Ten days after admission the count was: 9,650 white blood cells; eosinophiles, 5; polymorphonuclears, 65; stabs, 1; lymphocytes, 27; and monocytes, 1. Blood Wassermann and culture were negative on admission. Stools were negative for ova and parasites. Precipitin tests, taken five months after admission, Feb. 2, 1945, for trichinosis were negative. The National Institute of Health at Bethesda,

Md., reported a negative complement fixation test for trichinosis on the same serum. There was no known allergy present.

Course.—The child was given 2 Gm. sulfadiazine on admission and 1 Gm. every four hours with double doses of soda bicarbonate. Sulfathiazole ophthalmic ointment 5 per cent was applied to the eyes. Gentian violet 1 per cent was applied to the oral lesions. Supportive therapy, infusions, sedation, etc., was given (Graph A).

Two days after admission, the child was improved generally, but there was thick purulent sputum, probably due to involvement of the trachea and upper bronchi. The conjunctivae too,

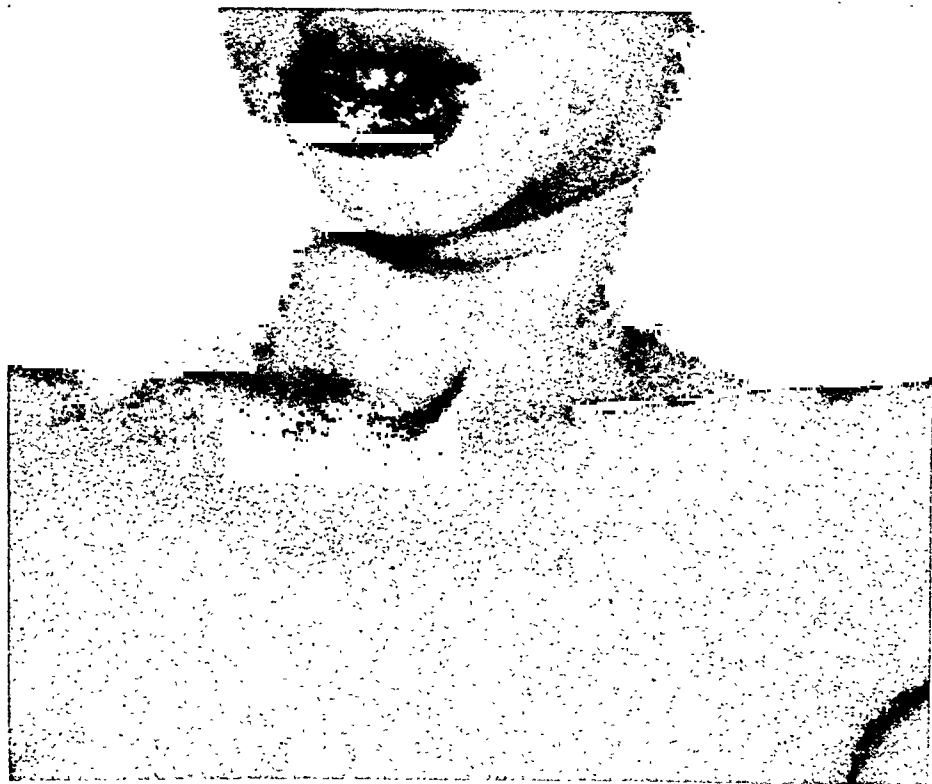


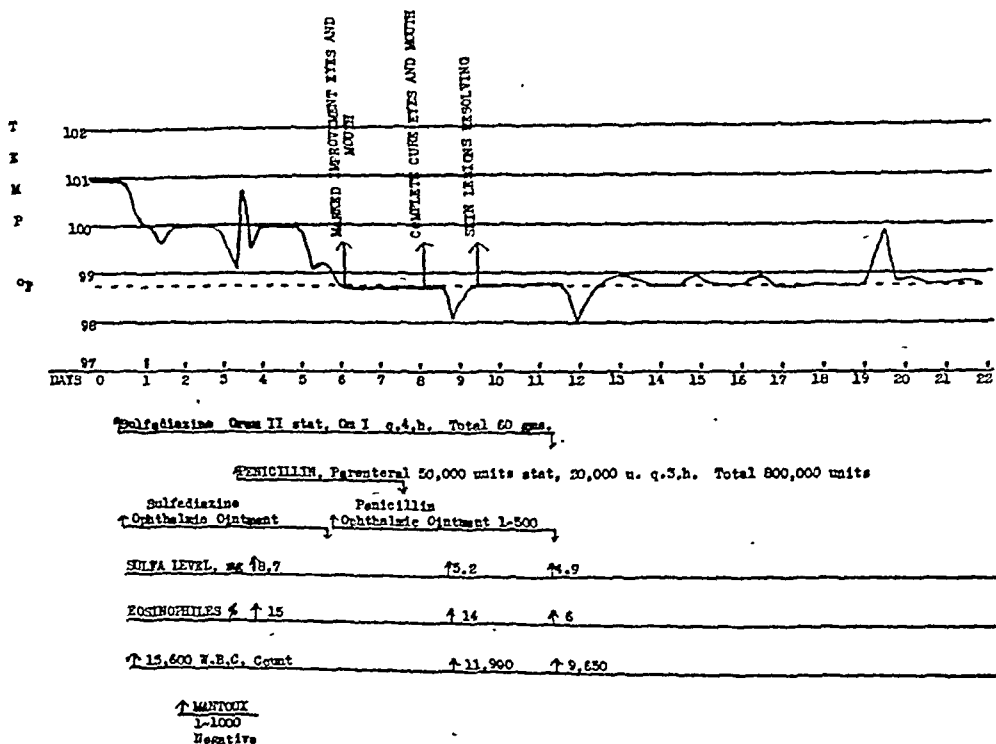
Fig. 6.—Photograph of another similar case showing skin distribution of residual pigmentation after resolution had begun.

as on admission, had marked inflammation and purulent discharge. The child's temperature was about 100° F. Since there was a possibility of the eye condition being a bacterial infection, either primary or secondary, it was decided to try penicillin therapy, because of the poor prognosis previously held for such eye cases. Struble and Bellows,¹⁶ in 1944, presented evidence of penicillin excretion into the various tissues of the eye. Therefore 50,000 units were given, stat, parenterally, and 25,000 units every three hours thereafter, starting on the third day after admission. Five days after admission, penicillin ointment (1 ounce = 500 u.) was applied generously to the eyes and mouth every three hours. After one day of local penicillin therapy, marked improvement of the eyes and mouth was noted. Most of the conjunctivitis had cleared. There were a few grayish sloughs on the tongue and buccal mucosa. The child ate well for the first time since onset of illness. There was no marked change in the skin lesions. They cleared nineteen days after onset.

COMMENT

Although this child had received sulfadiazine and parenteral penicillin, it is noteworthy that the more marked improvement was made soon after the use of local penicillin therapy. This was a dramatic change.

According to Sutton and Sutton¹⁵ the skin lesion in Stevens-Johnson disease heals in three to six weeks. In our study of twenty-one cases it was found that the skin cleared in at least three weeks in most cases, although one supposedly cleared in five days. In severe cases with recovery it usually takes three weeks for the eyes to clear, but in mild cases it takes only five to nine days.



Graph A.

This patient was admitted seven days after the onset of the illness. It was ten days after the onset that parenteral penicillin was started and twelve days after onset that penicillin was applied locally. After one day of local-penicillin therapy, the eye and oral lesions cleared and the temperature became normal. This patient's eyes and mouth were completely normal seventeen days after the onset of the disease, and the skin was normal nineteen days after the onset. The child was untreated for the first seven days.

It must be emphasized that this patient was extremely toxic when admitted. This was a severe case and the marked recovery three days after parenteral penicillin therapy and one day after local penicillin therapy can probably be

TABLE I

CASE	REF.	MILD OR SEVERE	PER CENT		TREATMENT AND TIME ALLOWED	TIME NECESSARY TO CURE EYES	SULFONAMIDE USED		EYE CULTURE	DID EYES CLEAR	TIME SKIN CLEARED
			ONSET	CURE			No	Yes			
1	1 (a)	Severe purulent	0	0	1. Metaphen 1-2500 q3h 2. Boric acid soaks 3. Atropine ointment	Began to clear in 6 days; completely clear in 9 days	No	Yes	<i>Staph. aureus</i>		
2	1 (b)	Mildly purulent	1	0	1. Boric acid soaks Sulfathiazole	18 days	No	Yes	<i>Staph. aureus</i>	Yes	
3	2		0				Yes				
4	3	Mildly purulent	1		Symptomatic	8 days	No		<i>Staph. aureus</i> ; hemolytic streptococcus	Yes	3 weeks
5	4 (a)	Severely purulent with erosions and vesicles	0	1	Symptomatic	Blind after six months	No			Blind	3 weeks
6	4 (b)	Severely purulent	0	1 and 4	1. Small; ineffective doses of sulfonamide from 26th to 30th day 2. Symptomatic	Blind (checked at 2 years)	Yes		Mixed	Blind	4 weeks with recurrence
7	5	Severe purulent with membranous lesions	1	0	1. Symptomatic 2. Local boric acid	Blind	No		<i>Staph. aureus</i>	Blind	8 weeks
8	6	Severe				Blindness and Chronic conjunctivitis	No			Blind	
9	7 (a)	Severe purulent with membranous lesions	0	0	1. Symptomatic 2. Local	30 days	No		No growth	Cleared	33 days

10	7 (b)	Mild		Normal	Neoursphenmino	5 days	No	<i>Staph. aureus</i>	Cleared	5 days
11	7 (c)	Mild		0	Symptomatic	1 month	No	Not done	Cleared	1 month
12	8 (a)	Severe purulent and ulcerative		0	Symptomatic	Blind	No	Streptococcus; staphylococcus;	Blind	79 days
13	8 (b)	Severe		0	Symptomatic	Blind	No	Mixed	Blind	
14	9 (a)	Severe		0	Symptomatic	Left, blind; right, cleared in 3 weeks	No	Leptothrix	1 blind; 1 clear	21 days
15	9 (b)	Severe				Blind	No	Staphylococcus	Blind	
16	10	Mildly purulent		0	Symptomatic		No		Cleared	3 weeks
17	11	Severely purulent					No	Staphylococcus		2 weeks
18	12	Severe		0	1. Neoprontosil 40 gr. per day for 4 days 2. Gentian violet 3. Metaphen	Inadequate data	No	Staphylococcus	Inadequate data	3½ weeks to 2 months
19	13	Mild		0	Supportive	3 weeks; recovered	Yes	<i>Staph. albus</i>	Yes	3 weeks
20	14	Moderately severe		0	1. Sulfathiazole 2. Tyrothricin for eye 3. Supportive	Began to clear in 8 days; cured in 3 weeks	No	Mixed	Yes	3-4 weeks
21	Case reported	Very severe	15	6	1. Sulfathiazole ophthalmic 2. Sulfadiazine 3. Penicillin local and systemic	11 days	Yes	Mixed; predominantly staphylococcus	Yes	3 weeks
						17 days (5 days after local penicillin)	Yes	<i>Staph. aureus</i>	Yes	17 days

attributed to the antibacterial action of these agents. However, this child had been receiving sulfadiazine for five days before penicillin and this, no doubt, influenced recovery. In three previously reported cases the patients recovered on sulfonamide alone.

We cannot say whether the therapy had any effect on the skin lesions but the nineteenth day was an early date for skin resolution to occur in a severe case.

The eosinophilia herein reported had not been seen in most of the cases tabulated (Table I), although Murphy¹⁰ recently reported a case with 6 per cent eosinophiles. A blood smear done on our patient in January, 1945, revealed 5 per cent eosinophiles still present.

On June 13, 1945, nine months after the onset of Stevens-Johnson disease, this patient was readmitted to the service with acute rheumatic polyarthrititis. Whether or not there is any etiological relationship is a matter of conjecture. It is noteworthy that there is a definite familial history of rheumatic fever.

On readmission there was no sign of any recurrence or sequelae of the Stevens-Johnson syndrome in the eyes or skin. There was no eosinophilia. The child, at time of writing, had an active severe rheumatic carditis and polyarthrititis.

SUMMARY

A case of a 9-year-old boy with Stevens-Johnson syndrome is presented.

1. In the past this disease in its typical, severe form was marked by but one serious sequela, that is, partial or total blindness due to eye involvement, possibly by bacterial agents. *Staphylococcus aureus* and sometimes mixed streptococcus and staphylococcus, are the most common bacteria cultured from the eye.

2. This patient was treated with sulfadiazine and penicillin, locally and parenterally, with decided improvement, which seemed to be related in dramatic time sequence to the use of penicillin, especially locally.

3. In a tabulation of twenty-one cases of erythema multiforme bullosa with mucous membrane lesions of varying severity, only five patients received adequate doses of sulfonamide or other antibacterial agents. In the seven most severe cases of the remaining sixteen, those that were typical of Stevens-Johnson disease, in which therefore, there was either purulent or membranous conjunctivitis, the patients were left with total or partial blindness.

4. It is suggested that such therapy as herein described, or modifications thereof, be used in the future to avoid eye complications. We do not know that penicillin is a "specific"; it may be, rather, an antibacterial agent useful against complications. Sulfonamides alone, in the past, prevented blindness, as did local Metaphen.

5. Six months after the onset of illness this patient was readmitted with acute rheumatic polyarthrititis.

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PENICILLIN IN THE TREATMENT OF CHILDHOOD GONORRHEA

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IT IS now common knowledge that penicillin has revolutionized the treatment of gonorrhea. The sulfonamides brought about a great improvement in this same field of therapy a short time ago, but their use is by no means completely satisfactory. Penicillin, used in adequate dosage, is curative for acute gonorrhea in its various clinical forms. The existence of penicillin-fast strains of the gonococcus in acute and previously untreated infections is doubtful.

Romansky, Murphy, and Rittman¹ reported the single injection treatment of acute gonorrhea in adult males, utilizing a beeswax-peanut oil suspension. With a dose of 150,000 units there were no failures in 75 cases. When the dose was 100,000 units, 93 of 100 cases were cured and the 7 failures responded to a second dose of 150,000 units.

Sako, Tilbury, and Colley² reported on single-dose penicillin treatment of chronic gonorrheal vaginitis in children. In this series, the penicillin was administered as a single dose of 100,000 units dissolved in 20 c.c. of sterile saline and injected intramuscularly. There was one failure in a group of 16 cases and this one patient was "promptly cured after she received eight doses of penicillin, 10,000 units every three hours."

In a recent paper, Cutting and associates³ discussed penicillin blood levels obtained when oral penicillin was administered with a variety of adjuvants and with enteric coatings. With these adjuvants and coatings as discussed, they treated 53 cases of acute gonorrhea, with a 72 per cent cure rate.

In the 21 cases of gonorrhea here reported, the children received from 100,000 to 300,000 units, depending on the route of administration. Only one case could be classified as really chronic, although three patients had been infected for more than three weeks. Thirteen were cases of vaginitis and of these ten were acute cases in which no previous therapy had been administered, while three were cases that had been treated with sulfonamides without bacteriologic cure. Eight were cases of acute anterior urethritis in boys less than 10 years of age. None of these had received any previous therapy.

When the clinical picture was typical and smears showed numbers of gram-negative intracellular diplococci, treatment was begun without confirmation by positive culture. Cure was accepted in girls only after three negative smears and three negative cultures were obtained. Where possible, the last smear and culture were made six weeks after treatment. In the boys three negative smears were accepted as evidence of cure, although in all but one instance there were also one or more negative cultures.

In every patient all smears and cultures were negative after treatment. Dysuria, when present, usually subsided within twenty-four hours, and always

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TABLE I. METHODS USED IN ADMINISTERING PENICILLIN

A. Saline Solution Intramuscularly

Eight girls and three boys received 100,000 units divided into six or seven equal doses, given at two-hour intervals. (Three received six doses.)

One girl and one boy received the same amount divided into eight equal doses given at two-hour intervals.

B. Beeswax-peanut Oil Suspension

One girl and two boys received a single intramuscular injection of 150,000 units.

One girl (chronic case, see text) received a total of 450,000 units; a first dose of 150,000 units, and a second dose, five days later, of 300,000 units.

*C. Oral Tablets With Sodium Citrate Buffer**

One girl (weight, 26 pounds) received 20,000 units every four hours for six doses.

One girl (weight, 30 pounds) received 25,000 units every two hours for twelve doses.

One girl (weight, 72 pounds) received 50,000 units every four hours for six doses.

One boy (weight, 26 pounds) received 40,000 units every four hours for six doses.

*These cases were treated under the supervision of Dr. Paul Gyorgy and are included through his courtesy.

within forty-eight hours. Discharge became progressively less in amount and was usually absent on the fourth or fifth day after treatment. In the boys it usually subsided in twenty-four to thirty-six hours.

In all of the cases in Table I there was prompt cure regardless of the method of administration. In the single case that qualifies as truly chronic there was a history of vaginal discharge of four months' duration. The patient had previously had at least two courses of sulfadiazine, each time followed by clinical relapse. She had also been receiving Theelin in a dosage of 5,000 units per week for three weeks. Smears were positive. She was given 150,000 units of the beeswax-peanut oil suspension, improved for a few days, and then had a recurrence of discharge. She was then given 300,000 units in the same form with prompt cure.

The single-injection use of a beeswax-peanut oil suspension of penicillin is simpler than multiple injection methods. When penicillin is plentiful and when the increased cost of the larger necessary dosage is not a factor, administration by mouth will undoubtedly be the method of choice.

SUMMARY

Twenty-one cases of gonorrhea in children were treated with penicillin by various methods of administration. Prompt cure was established in every case.

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PEMPHIGUS, SUCCESSFUL TREATMENT WITH PENICILLIN

REPORT OF A CASE

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TREATMENT of pemphigus is so unsatisfactory that any therapeutic agent which results in a remission or cure is worthy of description. Any conclusion from the treatment in one patient must necessarily be guarded. We desire to report the use of penicillin in a patient with proved pemphigus, in which there has been a remission, if not a cure, over a two-year period of observation.

No attempt will be made to survey the literature concerning the myriads of therapeutic measures used in the management of pemphigus, but several recent contributions are listed for reference.

Davis and Davis,¹ Wright,² Wolf and Lewis,³ Peck,⁴ Greenbaum,⁵ Tauber and Clarke,⁶ Topping and Knofel,⁷ Lever and Talbott,⁸ Oppenheim and Cohen,⁹ Lain and Lamb,¹⁰ Caro,¹¹ and King and Hamilton¹² have used successfully various forms of arsenic, vitamins, transfusions, and/or sulfonamide in treating pemphigus.

REPORT OF A CASE

V. B. (B 16601), a 4-year-old Jewish girl, entered Duke Hospital on Oct. 24, 1943, because of generalized vesicular lesions over the body of one month's duration. The first bullous lesion was noted on the left knee. The mother opened the bulla and treated it locally with sulfathiazole ointment. Three days later the child was taken to her physician and a diagnosis of impetigo was made. She was given ultraviolet therapy on the fourth, fifth, and seventh days, despite which the lesions continued to spread over the body. At this time the mother noticed some new papular and bullous lesions. One week after onset, the patient was seen, in consultation, by a dermatologist who advised oral sulfathiazole and 10 per cent ammoniated mercury locally. The sulfathiazole was discontinued in twenty-four hours because of nausea. On the ninth day after onset, numerous new bullae appeared, which were preceded by an erythematous papular eruption. Various calamine preparations were used to allay the pruritus. The lesions continued to spread and three weeks after onset, she was seen, in consultation, by another dermatologist who confirmed the diagnosis of bullous impetigo. Therapy at this time consisted of removing the crusts with soap and water followed by applications of a mercurial ointment. New bullae appeared daily in spite of therapy, and four weeks after onset, the entire body was practically covered with new and old lesions. (Figs. 1 and 2.)

Family history and past history were noncontributory.

Physical Examination.—The temperature on admission was 37.2° C. and the pulse rate was 124. She was well developed, well nourished, and the general physical examination was entirely negative except for the skin lesions.

Laboratory Findings.—Red blood cells, 5,270,000 per cubic millimeter; hemoglobin, 100 per cent; while blood cells, 30,000 per cubic millimeter. The differential formula was as follows: polymorphonuclears, 49 per cent; eosinophiles, 23 per cent; monocytes, 2 per cent; and lymphocytes, 26 per cent. Serologic tests for syphilis were negative. X-ray examination of the lungs and heart was normal. Patch tests to 20 and 50 per cent potassium iodide were

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Fig. 1.—Showing generalized bullous eruption.



Fig. 2.—Close-up of legs demonstrating bullae arising without a surrounding zone of erythema.

negative. Urine examinations were normal. Biopsy of the skin was compatible with pemphigus.* Phytopharmacologic test was 71 per cent (normal). Cultures from the crusted lesions showed a hemolytic *Staphylococcus aureus* and beta hemolytic streptococci.

Course in Hospital.—On admission the patient was placed on treatment with 1:4,000 potassium permanganate baths, 1 per cent gentian violet solution, and 5 per cent ammoniated mercury in cremalin. She was also given a course of sulfathiazole, consisting of 0.5 Gm. every four hours for six days. There was no improvement.

One week later she was given a course of naphuride, consisting of 0.5 Gm. every day for three days, without improvement.

Three days after the last dose of naphuride, she was given 10,000 units of penicillin intravenously. The following day she was started on a course of intramuscular penicillin, receiving 5,000 units every three hours for a total dosage of 116,000 units. During the course of penicillin, the temperature spiked from 38 to 39.5° C. She improved within one week and was discharged one month from the date of admission. At discharge, there were no new bullae, the old lesions were almost completely healed, and the patient was in good health generally.

Two years after discharge the patient was in excellent health and had developed normally, both mentally and physically. There has been no recurrence of the eruption. No conclusions can be drawn from a single instance, but in a disease so serious as pemphigus a trial with penicillin seems indicated.

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POOR EATING HABITS OF THE RUNABOUT CHILD: THE ROLE OF PHYSIOLOGIC ANOREXIA

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WELL-BABY clinics, in which the examining physicians have been fellows in pediatrics of the Mayo Foundation, have been held in Rochester, Minn., for many years. Although advice concerning the general run of behavior problems has been given in these stations for a long time, we are now inaugurating a definite attempt to prevent the development, among babies, of any habit disturbances. We hope that by careful study and supervision early in life, when habits begin, we can forestall difficulties and prevent later behavior problems based on them. One clear-cut example of such a preventable habit disturbance is found in the poor eating habits of some children of the runabout age. Because such children have responded to simple measures of treatment, we thought the situation should be emphasized.

Among 360 consecutive children from 1 to 3 years of age, who were attending the well-baby clinics, the mothers of eighty-two children, or 23 per cent, reported that the children had poor appetites and would not take a sufficient quantity of food. On physical examination these children were, in general, found to be in good health and to weigh close to the average for their ages and body builds. Moreover, they did not lack energy.

As was pointed out by Bakwin and Bakwin,¹ and by Aldrich and Aldrich,² toward the end of the first year of life, increase in weight is much less rapid than it is during the first six months of life. Correspondingly, there is need for less food for purposes of growth in the latter part of the first year and in the next few subsequent years. This results in a physiologic waning of appetite. A mother who is accustomed to having her baby demand large quantities of food is alarmed when this demand lessens or when the demand is even replaced by the child's refusal of much of the food. The mother usually responds by undue urging. Thus, a vicious cycle is likely to be started in which the mother insists that the baby eat more than he wants and the baby refuses to comply.

Another phase of the difficulty is encountered if the mother finds that the child does not take solid food readily, she may attempt to increase the amount of more easily consumed, liquid food. Thus, milk is given in larger quantities than before and the fat content of the diet is consequently increased. Few people realize that a quart of whole milk will supply almost one-half of the total daily calories needed by the runabout child.

With these facts in mind we advised the mothers of the eighty-two children mentioned in an earlier paragraph (1) to stop forcing food, allowing the child to eat what he wanted in a reasonable, but limited, time; (2) to offer mostly the foods that the child liked without undue coaxing or threats; (3) to remove any

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food left, without comment, and to offer no more until the next meal; and (4) to give no more than approximately 1 pint (500 c.c.) of milk in twenty-four hours. In some instances we advised that the milk be skimmed.

After several months we were able to re-examine sixty-five of the eighty-two children whose appetites had been reported to be poor. It was found that fifty-nine of them, or 91 per cent, had much better appetites than before and that the mothers no longer considered that the children presented feeding problems. Only six children, or 9 per cent of the sixty-five (only 1.7 per cent of the entire group of 360), were reported to have continued to have poor appetites.

On further examination it was found that the six children just mentioned were poorly adjusted in general, did not sleep well, and presented many other behavior difficulties. It was not surprising that they should also have poor appetites and be below the expected weight. Further work is being done with these children to help solve their somewhat complicated problems.

Since such definite benefit was obtained by these simple methods of treatment in a group of children who manifested disturbance in eating habits, we felt that even more good could be accomplished by preventive measures. Therefore, we now routinely warn mothers to expect their babies, in the second year of life, to consume a reduced amount of food and we advise them not to force the babies to eat more than they desire. In a later report, we intend to give the results of this preventive effort.

SUMMARY

Among 360 children, from 1 to 3 years of age, encountered in a well-baby clinic, eighty-two (23 per cent) were reported by their mothers to be troubled with anorexia. Simple directions were given to the mothers of these children, usually in one visit only. Several months later, sixty-five of the eighty-two children were re-examined. It was then found that the anorexia of 91 per cent of the sixty-five children had been cured. The remaining 9 per cent (1.7 per cent of the entire group of 360) presented multiple behavior problems.

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TICK PARALYSIS IN CHILDREN

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IT IS known to most physicians in the western part of the United States that tick paralysis is a dangerous disease that may prove fatal, particularly to children. Many cases of tick paralysis have been reported in the United States, but very few of these were from the eastern or central states. Since, in this country the disease is produced by two species of ticks, *Dermacentor andersoni* Stiles in the West and *Dermacentor variabilis* Say in the East, it is most prevalent in regions where these ticks are abundant. There are, however, many states where these ticks are present but in which no cases of tick paralysis have been reported. Kentucky is one such state and for this reason the following two cases are presented.

CASE REPORTS

CASE 1.—R. W., a 4-year-old white girl from Nicholas County, Ky., was admitted to the Louisville General Hospital on July 31, 1945. The chief complaint as given by her parents was that the day before admission "her legs gave away beneath her when she got out of bed." There was no pain or other complaint, but the mother noticed that when the child ate breakfast she made several ineffectual grasps before seizing objects. It was also noted that she was restless, and her pupils were thought to be large. She remained out of bed, but because the weakness of her legs had not improved she was brought to this hospital for treatment.

The past history was of interest in that the patient had a dog which was known to have had many ticks.

Physical examination revealed a well-nourished white female who was unable to stand alone but who otherwise appeared in no distress. Her temperature was 99.0° F., pulse 100, respirations 24, and blood pressure 92/60. Her hair was coarse and thick, and her skin was clear. The pupils were dilated, equal, and responded to light and accommodation. The fundi were normal and extraocular movements were intact. The neck was not stiff and no cervical masses were palpated. The following neurological findings were present: The child was unable to stand without support and would tumble forward when placed in an erect position. There was marked weakness of the lower extremities but no atrophy. Ankle and knee jerks were diminished bilaterally but abdominal reflexes were present. Asynergy of the upper extremities was noted on finger-to-nose test and on reaching for objects. Position sense and cutaneous sensibility were unimpaired.

Laboratory Examination and Course.—Complete blood count, urinalysis, sedimentation rate, blood Kahn, spinal fluid examination, Mantoux, and x-rays of chest and skull were all within normal limits.

On Aug. 1, 1945, the day after admission, there was marked weakness of the upper extremities. Biceps and triceps reflexes were diminished and ankle and knee jerks were absent. The lower extremities were completely paralyzed. No specific therapy was instituted. The next day a lumbar puncture was repeated and the pressure and the examination of the fluid were again entirely normal. Modified Kenny therapy was started but paralysis continued to progress.

On August 4, a fine papular rash appeared over face and nose and this was interpreted as *miliaria rubra*. The pupils were still dilated; there was complete paralysis of upper and lower extremities. Tendon reflexes were absent.

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On August 6, the child's condition was worse. The respiratory muscles, especially the intercostals, were involved and the child was restless and distressed. Paralysis of the muscles of deglutition became apparent and moderate cyanosis was present. At 11:00 A.M. she was placed into a respirator but synchronization was not satisfactory and she was removed promptly. Parenteral fluids were administered and prostigmine, 0.5 c.c. of 1:2,000 solution, was given every four hours with atropine sulfate, .15 mg. The patient was afebrile, complained of no pain, and remained mentally alert.

On August 7, an engorged tick was removed from the scalp in the occipital region. Further examination revealed enlarged occipital and cervical nodes on the right. Pupils were dilated and a right lateral nystagmus was present. All medication was discontinued.

Recovery was dramatic and within twenty-four hours the patient could walk, although the lower extremities were slightly weak. On August 9, forty-eight hours after removal of the tick, physical examination revealed only a slight weakness of the lower extremities which disappeared the following day. The tick was identified as a pregnant female, *D. variabilis*. (Fig. 1.) Patient was discharged on Aug 9, 1945.

One month later a letter from the mother reported that the child had no complaints



Fig. 1.—Tick, dorsal view.

CASE 2.*—W. M., 6-month-old white male infant whose home was Fort Knox, Ky., was admitted to the Norton Memorial Infirmary, July 12, 1943. The chief complaints as given by the parents were "general weakness and tick on the head."

The present illness began nine hours prior to admission. The child awoke at 2:00 A.M. whining and unable to take his bottle. The parents described his condition as "weak and limp all over." He was taken immediately to the Fort Knox Station Hospital where an examination revealed a large tick with its head buried in the patient's scalp. This was removed and the patient was sent home.

The patient continued to be fretful and hospitalization was thought advisable.

The past history revealed that the child had been visiting two weeks previously in Montana where Rocky Mountain Spotted Fever was prevalent. The remainder of the past history was noncontributory.

*Reported through the courtesy of Dr. M. A. Limper.

Physical examination at the time of admission revealed a well-developed child who appeared acutely ill. Skin examination was not remarkable. There was generalized flaccid weakness of the upper and lower extremities. The reflexes were not elicited and there was no stiffness of the neck. Spleen was palpable 1 cm. below the costal margin. The patient's temperature was 100.0° F. rectally.

Laboratory Examination and Course.—Blood examination revealed a white cell count of 12,200 per cubic millimeter with lymphocytes 55 per cent, and polymorphonuclear leukocytes 45 per cent; and a red cell count of 3,310,000 per cubic millimeter, with a hemoglobin of 10.2 Gm. per 100 c.c. Urinalysis was entirely negative. Lumbar puncture revealed no cells, negative globulin, 20 mg. per cent protein, 60 mg. per cent sugar and no growth on culture. Roentgenograms of the skull were interpreted as negative.

Feedings were given the first day by gavage. By 10:00 A.M. the following morning the patient was sitting up in bed playing. Temperature was never above 100.0° F. rectally. The patient was discharged June 14, 1943, fifty-four hours after admission, as entirely well.

Unfortunately the tick was not identified. Follow-up examinations to date have revealed the child to be perfectly normal.

Abbott¹ has recently made a complete review of the literature concerning paralysis produced by different species of ticks. The following discussion will be limited to the cases in the United States caused by the *D. variabilis*. This tick, the common dog tick, is found in the eastern and central states and in California. The life cycle consists of several stages of egg, larva, nymph, and adult. The incidence of the disease is greatest during the early summer months when the adult tick feeds. In the cases reported, the pregnant female tick has been found to be the causative agent. Gregson² and other investigators have shown experimental data to indicate that the tick injects the largest amounts of toxin on the fifth or sixth day. After ten days or less, the engorged tick drops from the host to the ground and deposits her eggs.

The first cases reported in the East due to *D. variabilis* occurred in Georgia³ and South Carolina⁴ in 1938. Since that time two more cases have been reported in each of these states⁵⁻⁸ and one case each in North Carolina,⁹ Texas,¹⁰ and New York.¹¹

The paralysis produced by the different species of ticks appears to be identical, however, as suggested by De Sanctis and DiSant'Agnese,¹¹ the prognosis may be better in those cases caused by the *D. variabilis*. In most cases the paralysis of the extremities is of the ascending type. As in Case 1, the child usually gets out of bed feeling well but discovers he is unable to walk. His efforts produce a marked ataxia and soon he is unable to stand. Ataxia of the upper extremities is also often present and unless the tick is removed the disease may progress, terminating in fatal respiratory paralysis. The pupils may become dilated and nystagmus develop. If the tick is removed before respiratory paralysis develops, recovery is usually complete and dramatic. In most cases the patient is afebrile.

As in tick paralysis produced by other species of ticks, the cases have been most frequent in female children below the age of 10 years. The site of attachment of the tick is often on the scalp, but may be beneath the breast, or in the axilla, vagina, external auditory canal, mouth, or any other exposed portion of the body.

In all but two cases reported in the United States produced by *D. variabilis* recovery has been rapid and complete following removal of the tick. Town-

send and Nash⁹ reported a case in a child who died two days after the removal of the tick. Ryan and Canning⁶ present a case in which weakness was present four weeks after the tick was removed.

The treatment begins with immediate removal of the tick and careful examination for multiple infestation. The tick must be removed with caution after engorgement has occurred, because there is danger of squeezing more toxin from the salivary glands into the patient. If the insect cannot be removed after killing with ether or turpentine, a small area around the site of attachment should be excised.

In Australia an antitick serum prepared from immune dogs is rather extensively used, but as yet there is none available in the United States for treatment of paralysis produced by the *D. variabilis*.

The remaining treatment is symptomatic. If respiratory paralysis is present, the patient may be placed in a respirator. However, Hamilton¹² stresses the danger of too early use of the respirator and reports a case in which death was accelerated by its use. Muscle training and massage are seldom necessary since recovery is usually complete.

Many theories concerning the cause of the paralysis have been discarded in favor of the toxin theory. As mentioned, it has been established that a neurotropic toxin is produced by the tick, but the site of production is not entirely clear.

Experiments in Australia have shown toxin to be present in saliva and eggs. Steinhaus¹³ found the toxin associated with the eggs of *D. andersoni*. As yet no reports have been made in which the investigator was able to reproduce paralysis with a tick taken from a patient.

The tick, *D. variabilis*, taken from the scalp of the patient in Case 1 was intact and seven days later began to lay her eggs. About 3,000 of these eggs were ground and suspended in 1 c.c. of saline containing 200 units of penicillin. This was injected subcutaneously into a male white mouse. Twelve hours later the mouse appeared definitely sick and could not use his right foreleg. There was a collection of fluid in this region of the leg. The mouse would feed and drink but was less active than the control.

In twenty-four hours the mouse did not use his right legs and refused food. The mouse died twenty-six hours after the injection of the eggs. The control mouse, also, did not use his right front leg, apparently because of local irritation but otherwise remained active and well. In seventy-two hours no remaining-involvement of the leg was noted.

Autopsy of the mouse revealed no gross abnormalities.

Five-tenths cubic centimeter of blood was removed from the dead mouse's heart and after 0.5 c.c. of saline was added, it was injected subcutaneously into another mouse. Except for local irritation the mouse's condition remained unchanged.

About twenty-one days after removal of the tick from the patient, it was placed beneath a screen on a shaved area of a young female rabbit. The tick did not feed and died two days later. The rabbit's condition remained good.

SUMMARY

1. Two cases of tick paralysis occurring in children from Kentucky are reported.
2. The flaccid paralysis that was produced in both patients disappeared rapidly after removal of the ticks.
3. In Case 1 the tick was identified as *Dermacentor variabilis* Say and its eggs were injected into a mouse producing its death.
4. In Case 2 the tick was not identified.

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ACUTE INFECTIOUS URTICARIA

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URTICARIA is not uncommon in children and is known to arise from a wide variety of etiological factors, the most common of which is food.

A review of medical literature for the past ten years reveals reports of urticarias from almost every known food, drug, chemical, as well as heat, cold, and emotional factors; but there are only a few citing bacterial infection as the causative agent and these mention only chronic urticarias.

Leriche¹ mentions two cases of chronic urticaria with recovery after appendectomies and one following a tonsillectomy.

Hansen-Pruss² reports a series of ten cases of chronic urticaria in adults, one associated with pyelitis; four with upper respiratory infection; one with peridental abscess; and four from gastrointestinal infection. He reports the isolation of the hemolytic streptococcus from each case.

Eichenlaub³ states that infection ranked second as the etiological factor in a series of fifty-eight cases of chronic urticaria.

Hopkins and Kesten⁴ report fourteen cases (one, a child) of chronic urticaria associated with chronic infection.

I wish to report a series of twenty-two consecutive cases of acute urticaria in children, associated with acute infection. I have observed many such cases since this detailed study was made, but these are not included.

The syndrome is characterized by urticaria, usually with angioneurotic edema, fever, and a demonstrable focus of infection. In this series the throat was most commonly the focus, with otitis media and pyelitis accounting for the remainder.

The degree of severity of the illness varied from the acutely ill child requiring hospitalization, to the mildly ill child with one or two degrees of fever and scattered urticarial eruption lasting two or three days.

Three of the more acutely ill patients and one with the milder type of urticaria are summarized.

CASE 1.—B. E., aged three years, was seen at home with an acute throat infection for which she was given sulfonamide therapy. After two days she seemed nearly well, but on the third day she became more acutely ill than before, and I was called back to see her. Her throat showed a spider web-like membrane and there was a large macular eruption more marked around the knees and elbows but scattered irregularly over the body. She was hospitalized and because of the previous sulfonamide therapy, which was considered a possible etiological factor, the only treatment in the hospital was parenteral fluids and local treatment of the urticaria. The temperature curve ran a septic course varying from 101 to 103° F. for five days. The tongue was bright red around the margin and at the tip, and the mouth was cracked in the corners. There was considerable edema of the hands and feet. The fingers and toes were a bright cherry red early in the illness, and desquamation of fingers and toes was extensive with complete loss of all the finger and toe nails. Blood and throat cultures were negative. Blood count showed 27,000 white blood cells with no increase in eosinophiles. Urine was negative throughout.

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Comment.—This was the first of the series and was not recognized as infectious urticaria until later cases occurred which were very similar. This was the only case in which sulfonamide therapy preceded the rash and in the remaining twenty-one it was used to eradicate the focus of infection without any effect on the urticaria.

CASE 2.—P. A., aged 2 years, was admitted to Contagious Hospital with a diagnosis of scarlet fever. The rash was urticarial in the beginning and became confluent to show a solid red coverage of the skin. There was marked generalized edema especially of the hands and feet. The temperature on admission was 103.6° F. rectally, and gradually returned to normal on the third hospital day with sulfadiazine therapy. Physical examination was negative except for the skin and a bright red throat; laboratory data showed a blood count of 26,400 white cells, with 35 per cent eosinophiles. The blood culture was negative. The throat culture did not show hemolytic streptococci. The urine was negative. The rash and edema gradually disappeared, and there was extensive *desquamation* in large flakes over the entire body with many lacerations from scratching. Calamine lotion was used locally to relieve itching.

CASE 3.—M. R., aged 7 years, was seen in my office complaining of fever, a sore throat, and a rash, which was urticarial in type and more marked on the extremities and around the waist. There was marked edema of the hands and feet. Temperature was 103° F. rectally. Sulfadiazine therapy brought the temperature to normal in three days and the rash gradually subsided in ten days. White blood count was 14,300 with no increase in eosinophiles.

CASE 4.—L. B., aged 10 months, was seen in the office with fever of 100° F. rectally, and a generalized urticarial eruption. Edema of the hands and feet was evident. Physical examination disclosed an acute otitis media on the right side. Sulfadiazine cleared the infection in two days and the rash disappeared in three days.

COMMENT

Three of the more acutely ill patients and one with the milder type of urticaria have been summarized. The greater majority of the twenty-two patients were either mildly or moderately ill. The characteristic picture was an urticarial eruption of varying intensity, usually edema of the hands and feet, fever, and most commonly an infected throat. Several of the throats had a peculiar spider web-like membrane over the tonsils.

LABORATORY DATA

With the assistance of Dr. Paul Beeson of the Department of Medicine of Emory University, an attempt was made to isolate the organisms and correlate the bacteriologic findings from the throat and blood cultures. Five blood cultures were negative. Six throat cultures taken under sterile precautions did not show the same organisms in any two cultures. The hemolytic streptococcus was found in only one culture. We had planned to culture a common organism and try to show skin sensitivity, but no common organism was found.

SUMMARY

1. Twenty-two cases of acute infectious urticaria were observed between February, 1943, and May, 1944.
2. Seventeen cases associated with upper respiratory infections were seen in the winter months, October to March, inclusive.
3. Thirteen patients were males and nine were females.

4. Fourteen were under 3 years and eight from 3 to 10 years of age.
5. History of allergy was negative in eighteen, positive in three, and unknown in one.
6. Three were acutely ill; nineteen were moderately or mildly ill.
7. Nineteen urticaries were associated with acute throat infections, two with acute otitis media, and one with pyelitis.
8. The three most acutely ill had white blood cell counts of 20,000 or above, with high neutrophile counts. One had a high eosinophilia. Blood cultures were negative in five. Throat cultures showed no common organism in six instances.
9. Two of the children had second attacks, three weeks and three months later, respectively.
10. A sulfonamide was considered a possible etiological factor in one, but the rash preceded the drug in the remaining twenty-one in which it was used to clear the focus of infection with no effect on the rash. Local treatment of the rash with calamine lotion seemed much more effective than ephedrine, adrenalin, histaminase or other systemic treatment.

CONCLUSIONS

A clinical syndrome is herewith described and presented in which acute urticaria occurred in children in twenty-two cases associated with bacterial infection. It would seem that the infectious process was the etiological factor in each case.

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ENTEROGENOUS CYST OF THE ILEOCECAL REGION

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ENTEROGENOUS developmental cysts of the ileocecal region are rare. Fifty-two cases have been previously reported,¹⁻³⁹ most of them in infants and children.

Congenital cysts arising from the alimentary tract have been described since 1856. The cysts may occur anywhere from the base of the tongue to the rectum, but they are most commonly found in the region of the ileocecal valve (Ladd and Gross,³⁷ Pachman,³⁴ Hughes-Jones,⁴⁰ Evans³¹). It is with such cases that this report is concerned.

Comprehensive reviews concerning congenital alimentary cysts have been made by Evans,³¹ Hughes-Jones,⁴⁰ Ladd and Gross,³⁷ and Poncher and Milles.⁴¹

Enteric cysts arise from and reproduce the structure of the normal intestinal wall. They are lined by intestinal mucosa and their walls contain varying amounts of fibrous tissue and smooth muscle. They may protrude into the bowel lumen or extend outside the wall depending on whether they grow submucosally or subserosally. Attachment to the mesenteric border is common. The cavities of the cyst are unconnected with the lumen of the bowel and contain mucus.

The embryology of such cysts has been the source of considerable discussion. Enteric cysts may be isolated remnants of the omphalomesenteric or vitelline duct and are, therefore, related to Meckel's diverticula (Meckel⁴²). Others believe the cysts arise from buds of endothelial tissue pinched off the primitive gut (Keibel,⁴³ Lewis and Thyng⁴⁴). A third theory is that they arise from the abnormal persistence of vacuoles present in the massed cells of the solid stage in intestinal development (Bremer⁴⁵). The first two theories explain most of the spherical cysts and diverticula, while the latter explains most of the true reduplications of the bowel.

The incidence of these cysts according to sex shows no significant predominance of females over males, although previous reports would indicate such. Of thirty-nine cases reported in which sex is given, there are twenty females and nineteen males.

Congenital ileocecal cysts occur almost exclusively in infants and children, although they have been described in adults. One report concerns a 62-year-old woman (Quensel⁸).

SYMPTOMATOLOGY

Enteric cysts may produce obstruction, pain, and bleeding. Symptoms of an acute obstruction are the most common. Less frequently there is abdominal pain either continuous or intermittent, a visible mass, constipation, and bloody stools. The latter phenomenon is rare. Often the symptoms simulate those of an acute intussusception, an acute appendicitis, or an appendicitis with abscess

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formation. Examination may disclose a palpable, freely movable tumor. Variable size of the mass upon subsequent examinations has been described (Rea³⁸). Tenderness and rigidity over the right lower quadrant with abdominal distention may be noted.

DIAGNOSIS

The diagnosis is usually made only at the time of surgery, or at the time of autopsy. The condition has not been diagnosed accurately up to this time. Differential diagnosis in infancy should always include intussusception. Other diagnoses to consider are appendiceal abscess, regional ileitis, granuloma of the cecum, twisted ovarian cyst, mucocele of the appendix, intestinal obstruction, and volvulus. X-ray examination may or may not disclose a filling defect in the region of the ileocecal valve.

TREATMENT

Operative procedures are the accepted means of treatment. Methods advocated include resection and anastomosis with or without a safety valve ileostomy above the anastomosis, enucleation of the cyst, evacuation of the cyst contents with or without permanent drainage, marsupialization either external or internal followed by escharotics, and by-passing the region of the cyst with an enterocolostomy. Of these, resection and marsupialization are the procedures of choice. Ladd and Gross³⁷ favor resection when possible. The recent literature emphasizes the importance of postoperative care in the form of adequate decompression and parenteral fluids including whole blood and serum.

CASE REPORT

A 14-day-old male infant was admitted to the hospital May 23, 1945, with complaints of vomiting and bloody stools. On the day of admission he vomited his feedings and had severe hiccups. About noon he had a large, loose stool containing mucus and old blood. At 6 P.M. he had a second large, loose stool containing much bright red blood. At that time he cried as if in pain and became quiet and listless. Past history disclosed that the infant had been delivered by midforceps after a prolonged labor. The birth weight was 8 pounds, 9 ounces. He spat up part of his breast feedings while in the newborn nursery. He lost weight from birth and at the time of admission was still 6 ounces under birth weight. Physical examination revealed a fairly well-nourished male infant with a soft, thin-walled abdomen. Peristaltic waves were visible in the epigastrium. A mass about 3 cm. in diameter was visible in the right lower quadrant which on palpation was firm, movable, and very slightly tender. Rectal examination revealed good sphincter tone, but bloody mucus was passed following withdrawal of the examining finger. The patient was seen by Dr. Stanley Gibson and Dr. Harold I. Meyer who thought he had an atypical form of intussusception.

Surgery was performed by Dr. Meyer who found a hard, 2.5 cm. mass in the terminal ileum. The tumor mass lay within the lumen of the bowel and could not be enucleated. No intussusception was found. A resection of the cecum, appendix, and terminal ileum with an end-to-side ileocolostomy was done.

Postoperative treatment included decompression, parenteral blood, serum, and fluids. On the fourth day after surgery a postpyloric routine of feeding was started, but because of the ensuing distention and vomiting, oral feedings were delayed another twenty-four hours. The subsequent course was then uneventful, and the infant was discharged on June 8, 1945. At the time of writing (September, 1945) the infant was in excellent health and weighed 16 pounds.



Fig. 1.—Surgical specimen showing the cyst lying in the opened terminal ileum. The cecum and appendix are at the left.

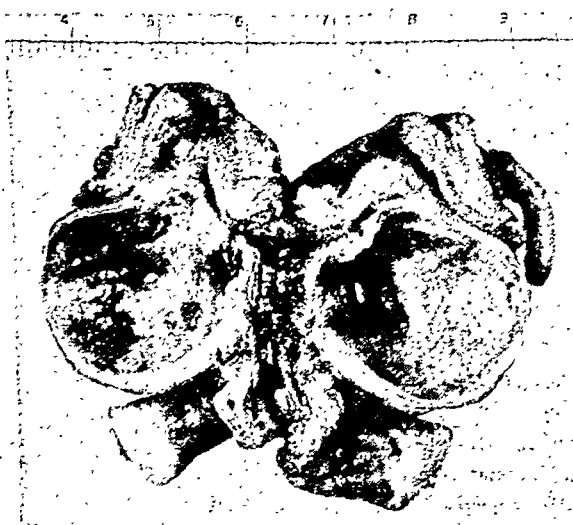


Fig. 2.—Surgical specimen showing the cyst and terminal ileum in longitudinal section. The cyst completely fills the intestinal lumen and is attached at the mesenteric border.

The pathologist reported a specimen consisting of a 4 cm. portion of terminal ileum and a 1 cm. portion of cecum with a normal appendix attached. A large obstructing cyst with a diameter of 2 cm. lay in the terminal ileum with its attachment at the mesenteric border (Fig. 1). The cyst cavity which had no communication with the bowel lumen contained glary yellow mucus. The wall of the cyst both internally and externally was smooth (Fig. 2).



Fig. 3.—Photomicrograph ($\times 2\frac{1}{4}$) of section through the cyst and ileum showing the cyst wall lined on both sides with intestinal epithelium. The cyst wall contains smooth muscle fibers and connective tissue.

Microscopic examination (Fig. 3) showed that the cyst wall was composed of smooth muscle fibers and a loose connective tissue stroma in which a few lymphocytes and an occasional polymorphonuclear leucocyte were found. At the angle of junction of the ileum and cyst the inner circular muscle fibers bifurcated, a portion going into the cyst wall and the other into the cyst base. The outer longitudinal muscle fibers were found only at the cyst base. The outer wall of the cyst had an epithelial covering continuous with and resembling that of the terminal ileum. The cyst cavity was lined with intestinal epithelium, columnar at the base, low columnar on the sides, and flattened at the apex. Beneath the epithelium at the base, the tissue had a glandular configuration with structures which resembled the Brunner's glands of the duodenum. Congestion was present throughout, and the lymphatic tissue showed hyperplasia.

Diagnosis: Congenital enterogenous cyst of the terminal ileum.

DISCUSSION

The patient presented demonstrates the difficulty of accurate diagnosis. The findings, although not entirely typical, warranted a preoperative diagnosis of acute intussusception. At operation an obstructing cyst was found in the lumen of the terminal ileum. This was resected with the adjacent bowel and a primary anastomosis between the ileum and the ascending colon was made. Examination of the surgical specimen showed no communication between the mucus-filled cyst and the intestinal lumen. Microscopically the cyst wall contained layers resembling those of the terminal ileum. The clinical, surgical, and pathologic findings in this case are comparable to those described by previous authors.

SUMMARY

1. A bibliography of reported cases of congenital enterogenous cysts of the ileocecal region is given.
2. The symptomatology, diagnosis, and treatment of these cysts are briefly summarized.
3. A case of a congenital enterogenous cyst of the terminal ileum is reported.

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MEDITERRANEAN ANEMIA (COOLEY) IN A NEGRO GIRL

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NO CASE of Mediterranean anemia (Cooley) in a Negro has, so far as we know, been hitherto reported. The present case appears to show the essential criteria of that disease.

S. B., was admitted Feb. 16, 1945, to the Children's Ward of Stanford University Hospital, because of frequent nosebleeds and anemia. She was born Feb. 15, 1939, in Arkansas. Her mother was dark-skinned, with typical Negro features. Her father was under treatment for syphilis in the Oklahoma State Hospital for Negro Insane. The mother had one stillborn child; a son who was feeble-minded and in the same institution as the father; and three other children who were alive and well. The latter have been observed by us and were typically Negro. The mother appeared to be in good health, but no Wassermann or other test for syphilis had been taken, to her knowledge.

S. B. had been admitted previously on or about Jan. 25, 1945, to the Palo Alto Hospital because of recurrent epistaxis of three years' duration, and anemia. Her spleen was found to be greatly enlarged. The first blood count there showed: red blood cells, 3,210,000; hemoglobin, 34 per cent; white blood cells, 17,600; neutrophiles, 53 per cent; normoblasts and metamyelocytes. Another count showed red blood cells, 2,790,000; hemoglobin, 31 per cent; white blood cells, 36,200; neutrophiles, 60 per cent; normoblasts and metamyelocytes. A transfusion was given and on dismissal, about February 9, the count showed red blood cells, 3,620,000; hemoglobin, 46 per cent; white blood cells, 19,250; and neutrophiles 52 per cent. During her stay her temperature varied between 99.0° and 102.8°; she had several nosebleeds and on one occasion some bleeding from the rectum. She was referred to us for further observation.

Our physical examination revealed a somewhat thin, listless Negro girl in no apparent distress. Pulse was 128; respirations, 24; temperature, 37° C. (rectal); and blood pressure 120/65. The head and face showed normal contours for her race. In the skin were many small scars with some keloid, and a small depigmented area on the forehead. There was a generalized slight enlargement of lymph nodes. The conjunctivae were pale; the sclerae were not icteric. The oral mucous membranes were pale. The tonsils were hypertrophied. A faint systolic murmur was heard at the left sternal border; no other cardiac abnormalities were noted. There was a large umbilical hernia. The liver extended about 4 cm. below the costal margin, was soft and not tender. The spleen extended to a level a little below the umbilicus, was hard and not tender. No other physical abnormalities were detected.

Several blood counts were made, of which the following by Dr. Harry A. Wyckoff is a typical example: red blood cells, 3,700,000; hemoglobin, 8.40 Gm. per cent (49 per cent Sahli); white blood cells, 7,500; neutrophiles, 63 per cent (of which 21 per cent were banded); basophiles, 3 per cent; lymphocytes, 26 per cent; plasma cells, 2 per cent; and monocytes, 6 per cent. There were 73 nucleated red cells per 100 leucocytes. Extraordinary poikilocytosis, anisocytosis and anisochromia, polychromatia and normoblastosis were present. Target cells and pessary forms were also found. No sickling was found in sealed cover glass preparations. Van den Bergh reaction: direct, negative; indirect, 1.08 units; icterus index, 8.

From the Department of Pediatrics, Stanford University School of Medicine.

Supplementary data.—The packed cell volume was 30. The mean corpuscular hemoglobin was 25.2 micromilligrams; the mean corpuscular volume was 76 cubic micra; the mean corpuscular hemoglobin concentration was 32 per cent. Platelets numbered 260,000 per cubic millimeter. The sedimentation rate was 19 mm. per hour (Cutler). Plasma proteins amounted to 7.9 Gm. per cent. Erythrocyte fragility: hemolysis began at 5.6 per cent sodium chloride solution and was complete at 3.5 per cent, essentially duplicating a normal control. No malarial plasmodia were found after 0.3 c.c. of epinephrine was injected subcutaneously. The Wassermann and Hinton flocculation tests were negative. Fecal urobilinogen excretion was determined by Dr. Robert S. Evans to average 312 mg. daily, which is greater than the normal adult output, and indicative of a hemolytic process. The blood belonged to Group O and was Rh positive. Urine analyses were essentially negative. Repeated tests for blood in the stool were negative. Several other tests for sickling were all completely negative.

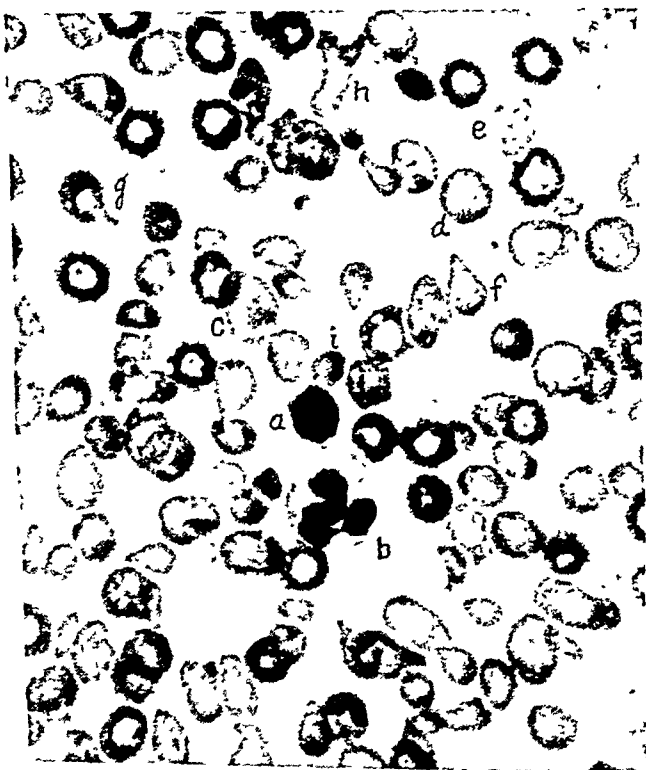


Fig. 1.—Blood smear; *a*, normoblast; *b*, granulocyte; *c*, macrocyte target cell; *d*, approximately normal erythrocyte; *e*, erythrocyte with marked irregularity of hemoglobin distribution; *f*, raindrop conformation; *g*, erythrocyte with tail; *h*, banana-shaped erythrocyte, serrated edge; *i*, microcyte.

Roentgenograms showed coarsening of bony trabeculae in the ribs, spine, pelvis, distal humeri, and bones of the hands. The skull was not, however, remarkable.

Physical examination and blood examination of the mother and two siblings living in San Francisco revealed no evidence suggestive of blood dyscrasia. Dr. E. P. Henry, Medical Superintendent of the State Hospital for Negro Insane in Taft, Oklahoma, kindly sent us blood smears from the patient's father and brother; neither of these showed abnormalities.

During her stay the patient had repeated nosebleeds. She received four transfusions without notable reaction and was dismissed March 11, 1945. At that time the red blood cells were 5,340,000 and the hemoglobin was 84 per cent (Sahli).

COMMENT

Sickle-cell anemia and spherocytic hemolytic anemia can, in our opinion, be ruled out in this case. As is evident in the accompanying microphotograph (Fig. 1), the blood was quite characteristic of Mediterranean anemia (Cooley). Morphologically, the red cells show the bizarre outlines with evidences of thinness, the irregularity of hemoglobin distribution, the tendency to fragmentation and to extreme variations in size, together with the great and persistent increase in nucleated cells (normoblasts and erythroblasts) which characterize that disease. The fragility of the erythrocytes was, however, approximately normal and did not show the increased span so often seen in Cooley's anemia. There was a moderate degree of hemolysis as shown by the fecal urobilinogen output. The bony changes, while not extreme, were of a character compatible with the disease.

Since no other members of the family were found to have a blood dyscrasia, speculation as to the origin of the patient's disease has no factual support.

SUMMARY

A case of Mediterranean anemia (Cooley) is described in a Negro girl.

EPIDERMOLYSIS BULLOSA HEREDITARIA

REPORT OF TWO CASES

EDNA ZELTNER MORTIMER, M.D.

CHICAGO, ILL.

THERE are few congenital skin diseases, and of these, epidermolysis bullosa is probably the least common. Recent discovery in the Armed Forces of the persistence of this disease into adult life has occasioned a renewed interest. We have recently seen our first two cases in infants.

The first case is that of a white male infant who was brought to the outpatient department on May 2, 1944, with a history of skin lesions present since birth. No definite diagnosis had been made and treatment had been without avail. It was stated by the baby's mother that some of the earlier lesions had healed while new ones, including some in the mouth, were constantly appearing. Delivery was at full term and spontaneous, and there were no neonatal difficulties. Treatment during the first three months of life included viosterol, vitamins B and C, an evaporated milk formula, and a heat cradle. Family history for similar skin lesions was said to be negative and consanguinity of the parents was ruled out.

Physical examination when the patient was first seen by us revealed a fairly well-developed and well-nourished 3-month-old white infant with widespread bullous eruption of the skin involving the face, trunk, genitalia, and extremities. Lesions were present on the mucous membrane of the mouth. Those on the skin were pinhead to 1 inch in diameter and were in various stages (Figs. 1 and 2). Some were bullae with clear fluid while others were hemorrhagic. Some lesions were crusted and in some areas the skin was denuded. White, ulcerated patches which bled easily were present on the tongue and buccal mucosa. Except for enlargement of the pectoral and inguinal lymph nodes, there were no other positive findings. A diagnosis of epidermolysis bullosa hereditaria (dystrophia) was made and the patient was admitted to the hospital for further study.

In the differential study, serologic tests (Wassermann, Kahn, and Eagle) were repeatedly negative. Dark-field examination of fresh bleb contents and lesions in the mouth revealed no cells or organisms. Complete blood counts, on admission and since, have been entirely within normal limits. The urine has always been normal. Many cultures of fluid aspirated from the lesions were negative except for one which produced a mold growth thought to be a contaminant. Blood chemistry studies, which included nonprotein nitrogen, urea nitrogen, creatinine, chlorides, vitamin A and C levels, calcium, phosphorus, sodium and proteins were all within normal limits. The blood cholesterol varied from a low of 100 during a remission stage, to a high of 284 during a stage of exacerbation, the accepted range of the normal values being 135 to 240. The significance of these findings awaits further elucidation. (An elevated basal metabolic rate is said by some¹ to be present in this disease.) Chest x-rays demonstrated no pathology.

The patient had been on regular infant feedings on which he had maintained a fairly good state of nutrition. (His weight at 1 year was 17 pounds.) Various ointments and solutions were applied locally, including boric acid, gentian violet, potassium permanganate, ammoniated mercury, and sulfonamide ointment; all without effect. A course of sulfathiazole by mouth and 60,000 units of penicillin daily for six days failed to alter the picture. X-ray treatment with 138 roentgen units to the trunk and extremities at weekly intervals was started in January, 1945, with no apparent effect.

The course of the disease in the hospital was characterized by periods of exacerbation and remission, summer being the most unfavorable season (Figs. 3 and 4). The baby im-

From The Children's Memorial Hospital.

proved greatly during the autumn months. He was kept in a tent at 70° F., and normal room humidity, and effort made to prevent trauma by handling him as little as possible. He wore no clothing except a diaper. Sulfathiazole ointment was applied to the lesions only when secondarily infected; otherwise no local treatment was being followed at the time of writing. He lost all of his fingernails and five toenails. Nikolsky's sign (outer layer of skin rubbed off by slight trauma) was highly positive. Areas of pigmentation and scarring were present on the skin where healing occurred, and leucoplakia where healing occurred in the mouth. Skin



Fig. 1.

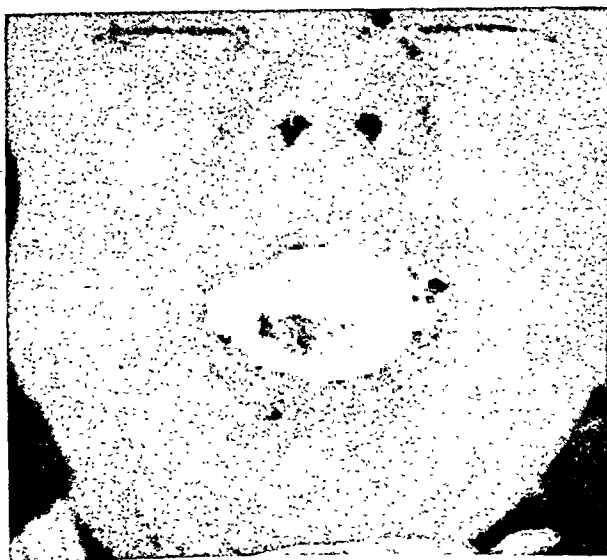


Fig. 2.

biopsy (November, 1944) revealed separation of the epidermis from the underlying tissue with only slight inflammatory reaction and loss of elastic tissue, compatible with a diagnosis of epidermolysis bullosa. Qualitative porphyria was not demonstrated.

The second case is that of a white male infant who was transferred to our hospital from Wesley Memorial Hospital where he was delivered on Sept. 30, 1944, at full term by low



Fig. 3.



Fig. 4.



Fig. 5.

forceps. His birth weight was 6 pounds, 12 ounces. At the time of delivery some redness and denudation were noted about the bridge of the nose. On the following day, blisters appeared on the face, trunk, and extremities, and some were seen about the ear. These later broke down and crusts formed. While older lesions healed, new ones appeared. The baby was a first child and the parents were well. There was no positive history for epidermolysis bullosa, but the maternal grandmother was said to have had a skin disease all her life. Physical examination of the patient upon admission revealed a 6-week-old boy weighing only 5½ ounces above his birth weight. He did not appear ill. A few small bullae were present on the face and some were healing (Fig. 5). There were fresh scars from previous lesions on the trunk, feet, and about the penis. The nails were intact. None of the lesions were hemorrhagic and none were seen in the mouth. Nikolsky's sign was positive. The spleen was palpable. A diagnosis of epidermolysis bullosa hereditaria (simplex) was made. Blood count was normal except for mild anemia. Blood cholesterol was 121. A skin biopsy in November gave findings identical with those described in the preceding case. No qualitative porphyria was demonstrated. The baby was discharged from the hospital in December, 1944, and was followed in the outpatient department until Jan. 16, 1945, at which time he was taken to St. Louis. During this period he made an excellent gain in weight. At the time of his final visit the lesions were in a state of complete remission with scars present on the face and trunk.

The literature on epidermolysis bullosa is rather meager. The first case was described by Von Hebra in 1870, but it was not until 1886 that the name epidermolysis bullosa hereditaria was attached to this disease entity. The etiology remains obscure, though various hypotheses have been advanced. Heredity appears to play an important role and consanguinity of parents may predispose. It may occur in any race, the males being more susceptible.

The significant histopathologic change observed in almost all cases is separation of the whole of the epidermis from the corium.²

Typically, the disease is present at birth or appears shortly afterward. It is a chronic disease of the skin characterized by blisters which usually result from mechanical irritation. The lesions start as bullae which may be pinhead to goose egg in size and are serous, sometimes hemorrhagic. They may occur anywhere on the body but the sites of predilection are the fingers, toes, knuckles, ankles, and elbows. The lesions may rupture and crust over, in some cases leaving scars and pigmentation; often they become secondarily infected. There are exacerbations and remissions and the condition is aggravated by heat, moisture, and trauma. The disease continues throughout life, although in later life symptoms ameliorate. Occasionally puberty marks its disappearance and pregnancy may interrupt its course.

Two major types of epidermolysis bullosa are described, the "simple" and the "dystrophic."³ The former runs a more benign course in which the lesions are seldom hemorrhagic and without involvement of mucous membranes or nails. Our first case is quite characteristic of the dystrophic type and the second of the simple type.

Porphyria has been described in some cases.^{4, 5} Nikolsky's sign¹ is usually positive. The general nutritional state of the infant is not noticeably affected and prognosis for life is generally good.

The histologic changes in the skin seem to represent a quantitative change in the response of the skin to trauma, heat, and moisture.⁶

Treatment remains empiric and prophylactic.

SUMMARY

Two cases of epidermolysis bullosa hereditaria, one representing the simple type and the other the dystrophic type, have been presented. The etiology remains obscure. Empiric treatment modifies the course only slightly.

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PITUITARY DWARFISM?

SPONTANEOUS CORRECTION

I. P. BRONSTEIN, M.D., CHICAGO, ILL., AND
EDUARDO CASSORLA, M.D.,* SANTIAGO, CHILE

THE diagnosis of anterior pituitary dwarfism is made, with but few exceptions, by the exclusion of other causes for arrested development, rather than by positive proof. The positive diagnosis of this condition by roentgenologic intra- or extrasellar tumors is rare.¹ The diagnosis is therefore a presumptive one based on the following clinical evaluations: (1) understature; (2) symmetrical proportions; (3) sexual infantilism; (4) delayed epiphyseal closure; (5) history of normal growth to about 2 to 3 years of age with sudden deceleration in rate of growth thereafter. The undersize is usually apparent by the fifth to sixth year of age.

The use of preparations of the anterior lobe of the pituitary gland, containing the growth promoting principles, in children with varying subnormal rates of growth has met with unsatisfactory results in our experience.†

We were interested in some practical and inexpensive approach to the treatment of undersized children with pituitary growth hormone. We, therefore, adopted a procedure whereby 100 c.c. of pituitary growth material were used in addition to the simultaneous administration of thyroid extract, which supposedly intensifies the action of the growth substance. The results were disappointing and most parents refused to expend further sums for treatment. In the case of a classical Lorain dwarf having a calcified intrasellar mass, approximately 1,000 c.c. of pituitary growth hormone were used with poor results. This patient received heretofore untried single high doses of 10 c.c. of pituitary growth hormone intramuscularly.

This report is concerned with a case of a seemingly spontaneous resolution of a presumptive classical hypophyseal dwarf during late adolescence, in which the girl attained a low normal height and complete sexual development. No treatment was instituted during the entire period of observation which extended from June, 1936, to February, 1942.

M. A. was first seen at the age of 12 years because she was not growing. There were no other complaints. She was born in November, 1921, to older parents of Swedish ancestry, the father being 40 and the mother 38 years of age; both were in good health. There were seven other children, all boys of good development; and their heights, as well as those of the parents, were toward the tall side. The members of the mother's and father's families were also tall. There was no family history of stunted growth or sexual disturbances.

The patient was a full-term baby weighing 6½ pounds at birth. Her height at the time of delivery was not recorded. No statural measurements were available prior to her entrance into our institution. She had been well since birth, except for measles. The dietary history was inconsequential.

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†The administration of chorionic gonadotropins in male and gonadal substances in male and female children has been accompanied by partially successful results.

When first examined, she was 46½ inches tall and weighed 44 pounds, approximately 11 inches and 37 pounds below the averages for her age. She was a normally proportioned girl in good health. When she was 15 years old, there were no secondary sex characteristics and the external genitals were infantile although structurally complete. Rectal examination revealed a very small cervix and almost indistinguishable corpus uteri. Complete



Fig. 1.—M. A.: Age, 14½ years; weight, 54 pounds; height, 50½ inches.
Age, 20½ years; weight, 103 pounds; height, 59 inches.

endocrinological investigation was negative; nonfusion of the epiphyses was noted. Hormonal studies did not reveal any assayable estrogens or gonadotropins. At the age of 14 years and 11 months, she had a mental age of 12 years and 9 months, and an I.Q. of 89. (Weight 54 pounds, height 50½ inches.) At the age of 17 years and 4 months, her mental age was 13 years and 8 months, and her I.Q., 91.2. She was socially and emotionally immature for her age. Her personality traits were apparently related to the physical underdevelopment. At 17 years of age there was an increase in the rate of growth, and at 22 years of age she had attained a low-normal height. (Height, 59½ inches; Weight, 94 pounds.) At 18 years of age the first secondary sex characteristics were noticed, breast enlargement being the initial change. Pubic and axillary hair appeared at 19, and menses at the age of 20 years. In 1944, when last seen at the age of 22 years, she was engaged to be married.

COMMENT

Our patient presented proportionate dwarfism, sexual infantilism, and delayed osseous development, cardinal signs present in cases conforming to classical anterior hypophyseal deficiency (Lorain type).

While statural underdevelopment is not particularly difficult to recognize, nevertheless in the diagnosis of pituitary dwarfism, other causes for retarded development must be eliminated by an exhaustive examination. It is to be emphasized that although one may be reasonably sure of the diagnosis, doubt always remains except in infrequent cases in which the hypophysis has been removed or known to be destroyed, when necropsy verifies the report, or there is roentgenologic evidence of a pituitary tumor. The diagnosis of this condition is then, with rare exceptions, a presumptive one. If there were an efficacious pituitary growth hormone, then definite and continuous response to it would constitute evidence of previous growth deficiency.

Our case illustrates progress without therapy. Had treatment been instituted, pituitary growth hormone would have been credited for the result. Although our patient presented all the criteria of deficiency of the growth and gonadotropic factors, yet she might be looked upon as a case of remarkably delayed puberty which underwent spontaneous correction.

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The Academy Study of Child Health Services

THE ACADEMY STUDY

WHY A STUDY?

The Study arose from the realization, primarily on the part of pediatricians, that if children are to have the care they need in the postwar era, thorough and systematic planning to provide that care is essential. Furthermore, it is felt that the responsibility for such planning rests unquestionably on the physicians themselves. They are the ones who know what constitutes good care; they are the ones who for the most part provide that care; and they are the ones who should develop and conduct the program. But before any well-founded plans can be evolved, a study is required to determine what services are available and to evaluate the quality of those services.

One of the primary purposes of this Study is to stimulate local groups to discover for themselves the needs within their own communities and to evaluate existing facilities.

The Study is important. Unless physicians undertake the task, others less well qualified will, as indicated by various bills now before Congress.

WHAT IS IT?

The content of the Study falls into four categories:

1. *Hospital Facilities.*—Detailed information on pediatric care will be sought from all hospitals: general, pediatric, and maternity, and special hospitals such as convalescent homes, tuberculosis sanatoriums, and others.

2. *Community Health Service, Public and Private.*—The Study will cover the extent and quality of general health services such as child-health conferences, school-health service, child-guidance clinics, immunization program and public health nursing.

3. *Distribution, Qualifications, and Activities of Professional Personnel.*—Data will be collected from pediatricians, general practitioners, and specialists who care for children. Information will be sought in each community concerning availability of physicians and procedures essential for medical care, such as transfusion, provision for intravenous fluids, availability of artificial respiration and oxygen, and essential laboratory determinations.

4. *Pediatric Education.*—Basic to this Study is an evaluation of pediatric education. A study of the sixty-six medical schools throughout the country will be made to determine the quantity and quality of training in pediatrics. This division of the Study is not a part of the State Programs but will be carried out on a national basis by a special committee appointed for this purpose.

EXPECTED RESULTS

At the conclusion of the Study a report will be prepared which will be available to all who care to use it. It will be a collection of factual data which will be used by the Academy of Pediatrics as a basis upon which sound recommendations for medical care programs can be made.

CONDUCT OF STUDY

The members of the American Academy of Pediatrics are committed to carry out the Study of Child Health Services.

The responsibility for the organization and conduct of the Study within each State lies in the hands of the Academy State Chairman, who with the help of a full-time Executive Secretary will carry out the program and correlate all the many activities involved. However, as this is primarily a pediatric study, it is the pediatrician who is the key to the problem and it is upon his full cooperation that the success of the study depends.

NORTH CAROLINA STUDY OF CHILD HEALTH SERVICES

ARTHUR H. LONDON, JR., M.D., JOSEPH LACHMAN, M.D., AND ESTHER MILLER

With the end of the war, the American Academy of Pediatrics has instigated a nationwide Study of health and medical services for children preparatory to developing a sound program of postwar activities. It was felt that a Study, to determine "who" and "what" is currently available for the medical care of children, was the only basis on which future planning could be undertaken.

It was determined at the outset that the State would be the best unit for study and that a pilot study in one state should be conducted as a field trial prior to any large-scale planning. In selecting North Carolina as the test state several criteria were considered: geographical size which would permit rapid communication and transportation, distribution of population, sufficient facilities and services to provide a proving ground for the study but which could be examined in a period of a few months, proximity to the central office in Washington, cohesiveness of the State Pediatric Society, and willingness of the pediatricians to assume the responsibility which attends the test study of a nationwide survey.

The annual meeting of the North Carolina Pediatric Society was held at Roaring Gap on Sept. 7 and 8, 1945. Dr. Warren R. Sisson, Chairman of the Academy Committee on post-war planning, and Dr. Katherine Bain, of the United States Children's Bureau who is on loan to the Academy to assist in the study, presented the outline of the study and acquainted the pediatricians of the State with its objectives. After a free discussion those present agreed unanimously to undertake the study. A full-time executive secretary was secured; on October 15 offices were set up in Raleigh in space made available by the State Board of Health and plans for the administration of the study were prepared.

The state was divided into districts and the pediatricians located in each district were asked to assume responsibility for: (1) acquainting the physicians in the area with the purpose of the study; (2) assisting with the collection of certain hospital information; and (3) completing schedules of information concerning their own practice. A personal visit was made by the executive secretary to each pediatrician in the state during the course of which his responsibilities and duties were discussed in detail. Letters were prepared for the signature of the pediatricians who then sent them to the physicians and hospital superintendents in their districts. Pediatricians also visited the county medical societies in their respective areas at which time the meaning of the study was explained.

Following the interpretation of the study by the pediatricians to medical and hospital personnel, a general publicity campaign was started. Articles appeared in medical journals, newspapers, and the bulletins of various voluntary groups such as the State Tuberculosis Association and the state office of the National Foundation for Infantile Paralysis. An "advisory committee" of representatives of voluntary and professional organizations interested in child health was formed. A meeting of this committee was held early in the course of the study at which almost every organization represented made plans to inform their constituent local agencies of the background and purposes of the study.

When the necessary introductory work had been accomplished, the executive secretary then proceeded to send out the schedules. The pediatricians were asked to assist in the follow-up work necessary to bring in the schedules. This involved telephone calls and/or visits to public health offices, physicians, and hospital superintendents and constituted an important part of the job.

The trial schedules which were distributed in North Carolina may be described briefly as follows:

1. The schedules for hospitals included questions on the type and extent of accommodations for children, the type of staff available for treatment of different cases, the number of patients actually cared for in one day, the presence and use of laboratory services, the method of formula preparation, and the number of communicable disease cross-infections during one year. Special forms were designed to elicit information from tuberculosis, orthopedic, and nervous and mental hospitals, and also convalescent homes.

2. The questions for physicians in private practice concerned postgraduate and hospital training, designation of a specialty, availability of consultant services, and a one-day record of child patients treated. For dentists in private practice a similar schedule was prepared. The pediatrician's schedule called for more detailed information including the child and family case load, and a month's record of services to children in various age groups taking into consideration activities other than private practice.

3. The forms to be completed by local public health departments and other community health agencies were planned on a comprehensive basis. Annual data were sought on the type and number of staff, and the quantity of various services rendered children in medical well-child conferences, dental clinics, mental hygiene clinics, physically handicapped and communicable disease clinics and other school health and public health functions.

By February 15 the initial section of the study, the collection of data, had for the most part been completed. Schedules sent to the various groups have been completed and returned with the following gratifying high percentages:

QUESTIONNAIRES	PERCENTAGE OF RETURNS
Pediatric, General, and Other Hospitals	92
Special Hospitals:	
Tuberculosis	95
Orthopedic	67
Nervous and Mental	92
Convalescent Homes	100
Physicians	53
Pediatricians	92
Dentists	68
Public Health Districts	100

During the survey it has been necessary for the pediatricians in North Carolina to bear in mind the two purposes of the test study in their state: (1) to acquire data pertinent to the aims of the study, and (2) to determine the type of question which could and would be answered by professional and hospital personnel. It is believed that the majority of questionnaires returned are sufficiently complete in answers to enable statistical experts to set up adequate tabulations and meaningful analyses. On the basis of comments and suggestions received and general difficulties encountered in acquiring data on certain subjects, the schedules have been revised so that there will be less chance for misinterpretation in the future. The questions included in the schedules have been made as foolproof, self-explanatory, and simple as possible so that record-scanning and file-hunting on the part of those providing the answers are cut to the minimum. It is essential that the pediatricians accept responsibility in cooperating with the state chairman and executive secretary in the completion of the more difficult and detailed schedules.

These then are the accomplishments to date: a fairly high percentage of returns on all schedules, a high degree of completeness in the information supplied, and valuable suggestions for the revision of the questionnaires. This has been accomplished in a state which has been overstudied rather than understudied, and it has taken four and one-half months instead of the anticipated six months. Whatever else has been proved, experience in North Carolina has shown that the study can be conducted in any state with a reasonable assurance of success.

The following points based on certain experiences in this, the experimental state, may contribute to the successful administration of other state studies. Support should be sought prior to the opening of the study from all state professional groups whose members will be asked to furnish information, especially state medical and dental societies. Explanatory material should be prepared for use by these professional organizations on all levels. The fact should be emphasized that this is a study requiring the cooperation of all those who provide a facility or service for the medical care of children. This point should be stressed also by the executive secretary in his contacts with all medical, public health and hospital personnel.

General publicity directed to the state as a whole proved of great value in gaining acceptance of the study. State headquarters of all groups interested in medical care for children should be made aware of the Academy program in order to enlist support of their state and local groups. It must be borne in mind, however, that information concerning the study must reach the professional organizations first, especially the pediatricians, before any releases are made for general publicity.

Comprehensive as this study is, the data can be collected. It is a job which entails publicity, administration, coordination, personal contact, and hard work. Its success depends not on the efforts of one individual or group. Only with the cooperation of all groups solicited for data and all groups which will eventually utilize the information gathered can the study be assured of a successful conclusion.

The Social Aspects of Medicine

The following article is abstracted from a report prepared for the Children's Bureau from original Russian sources by Anna Kalet Smith.

We are indebted to the Bureau for permission to abstract the report.

HEALTH AND WELFARE SERVICES FOR MOTHERS AND CHILDREN IN THE UNION OF THE SOVIET SOCIALIST REPUBLICS

FROM ORIGINAL RUSSIAN SOURCES

BY ANNA KALET SMITH

A. Branches of the Government of the U.S.S.R. concerned with health and welfare services for mothers and children

1. General legislative and administrative branches

Health and welfare services for mothers and children in the U.S.S.R. (Union of the Soviet Socialist Republics) are organized on a legal basis and are administered by agencies of the Government—Federal, Republic, or local. A description of the country's legislative and administrative organization, as it relates to these services, may help to understand the operation of the system. The country's legislative and administrative machinery is prescribed in the Constitution of the U.S.S.R.

Supreme Council of the U.S.S.R.

The federal laws are enacted by the Supreme Soviet of the U.S.S.R., often called Supreme Council (which is the translation of Soviet). The composition and functions of this Council are defined in the Constitution. The Council consists of two chambers: (1) the Council of the Union, elected by citizens according to election districts and on the basis of one representative for each 300,000 inhabitants; and (2) the Council of Nationalities, elected by citizens according to certain territorial units of the country so as to give representation to the various national minorities. The members of the two Councils are elected for four years. Both Councils have equal rights.

*Council of the People's Commissars of the U.S.S.R.**

The Council of the People's Commissars of the U.S.S.R. consists of the directing heads of the various departments of the Government, such as finances, justice, public health, education, interior, trade, and industry. The members of this Council are selected by the previously-mentioned Supreme Council.

The Council of the People's Commissars of the U.S.S.R. is the executive and administrative branch of that country's Government. It issues decrees and regulations for the administration of laws enacted by the Supreme Council and watches over their enforcement, and it coordinates and directs the work of the various Government departments.

The Council of the People's Commissars is directly responsible to the Supreme Council.

Each of the sixteen republics enumerated in the Constitution, edition of 1944, as comprising the U.S.S.R. has its own Constitution, Supreme Council, and Council of People's Commissars; the composition and functions of these two bodies are in general similar to those of the U.S.S.R.

The republics constituting the U.S.S.R. are divided into provinces; some republics also have territories; others include also autonomous republics or autonomous provinces, both populated mostly by national minorities. All provinces and the larger cities are divided

*Since the preparation of the present report the use of terms "commissar" and "commissariat" has been discontinued and "minister" and "ministry" have been substituted. This took place on March 15, 1946, by resolution of the Supreme Council of the U.S.S.R.

for administrative purposes into districts. Each province, territory, provincial district, city, city district, and village is governed by a "council of workers' deputies," that is, representatives of the employed population. The council is elected for two years. The rules for the election of the members of the council are prescribed by the constitution of the individual republic. The council directs the work of the local government; it decides on the local budget; it directs the local economic and cultural activities; and takes measures for the enforcement of laws and for safeguarding the citizens' rights.

The council's executive and administrative branch is the executive committee elected by the council from among its members.

2. Public-health authorities

Commissariat of Public Health of the U.S.S.R.

The health work for mothers and children in the U.S.S.R. has been under the general direction of the Commissariat of Public Health since 1936, the year of the Commissariat's organization. Prior to that, the commissariats of public health of the constituent republics had charge of this work within their respective territories. The main purpose in creating this Commissariat was to coordinate health work in the various republics of the Union.

Among the functions of the Commissariat, as announced in 1938, were the direction of the public-health work, including health services for mothers and children in the entire country; the formulation of policies and standards of health work; the promulgation of rules for the administration of laws and decrees on the subjects of health; and the enforcement of this legislation.

Département of maternity care

The Commissariat of Public Health of the U.S.S.R., as reorganized in 1940, has a Department of Maternity Care.

Department of child health services

The Commissariat's department of child-health services issues regulations for the work of various child-health services, such as children's hospitals, sanatoriums, day nurseries, child health centers, and milk stations; it has general direction and supervision of this work and of the medical care of children in schools, kindergartens, orphanages, and other institutions.

Advisory committee and advisory council of medical men

The Commissariat of Public Health of the U.S.S.R. is assisted by an advisory committee consisting of the Commissar, the vice-commissars, a representative of the medical profession, the head of the bureau of finance of the commissariat, and one private citizen, appointed by the Commissariat. The committee meets regularly and considers, under the chairmanship of the Commissar, various phases of the commissariat's work, such as enforcement of laws, examination of reports from the local public-health branches, issuing of regulations, and appointment of staff. The decisions of the committee, if approved by the Commissar, are issued in the form of orders. In case of difference of opinion between the committee and the Commissar, the opinion of the Commissar prevails. Appeals may be taken to the Council of People's Commissars.

The Commissariat is also assisted by an advisory council of medical men without administrative responsibility, which advises the Commissariat on matters relating to public health, medical education, preventive and medical treatment, and nutrition. The council's decisions go into effect upon approval by the Commissar or the first vice commissar.

Council on curative and preventive treatment of children and council on maternity care

Early in 1943 the Commissariat of Public Health of the U.S.S.R. issued regulations for the organization of a council on curative and preventive treatment of children as an adjunct to its own office and of similar councils at the commissariats of public health of the republics constituting the Union, and at the departments of health in provinces and territories. The purpose of these councils is to obtain the help of qualified pediatricians

in the reduction of children's morbidity and mortality. These councils examine the plans for child-health work by the above-mentioned authorities and the current problems of such work; they participate in the investigations of child-health services; they help to determine the extent of compliance with the orders of the public-health authorities; they formulate measures for checking disease among children, and take active part in conferences on child-health work. Early in 1944 one of the organs of the Commissariat of Public Health reported that such councils were operating in the majority of cities and that they, as shown by the reports of the meetings, proved very useful.

The Council on Maternity Care was appointed late in 1943 or early in 1944 by the Commissar of Public Health of the U.S.S.R. To this Council, consisting of more than 80 medical scientists and health workers, has been assigned the task of considering measures for improving maternity care and gynecological treatment.

Commissariats of public health in the republics

Each of the republics constituting the U.S.S.R. has a Commissariat of Public Health which directs and supervises the health work in the republic, including the services for mothers and children. At the head of each Commissariat is a Commissar, who is usually assisted by two or more vice-commissars, by an advisory body for administrative purposes, and by a scientific medical council. One of the vice-commissars has charge of the child-health services.

The Commissariat's advisory Committee ascertains whether the Commissariat is doing the work it is expected to do; it also examines the reports from the local health departments, and the orders issued by the Commissar. The committee's recommendations or decisions are presented to the Commissar, who issues them in the form of his own orders.

The Commissariat also has a medical council whose functions are somewhat similar to those of the council attached to the Commissariat of Public Health of the U.S.S.R.

Departments of public health in the provinces, territories, provincial districts, and cities

The provinces and territories of the R.S.F.S.R.* each have a department of public health including services for mothers and children but excluding the work of the institutions which are under the direct control of the National Government or that of the republic in which the province or territory is situated. No separate division of services for mothers and children is mentioned in the decree of 1939 on the reorganization of the departments of health.

Each of the districts into which the provinces are divided is required by law to have a department of health. One of the assistant directors has charge of the child-health work, including medical care of children in schools and in institutions.

The cities have their own departments of health; in larger cities which are divided into administrative districts, each district has such a department.

The provincial and city departments of health are supervised in administrative matters by the executive committees of the previously-mentioned councils of workers' deputies; in their medical and public-health work the departments are expected to follow the orders of the Commissariat of Public Health.

B. Health and welfare services for mothers and children

1. General characteristics of the system

The Russian system of maternal and child care is intended to serve all mothers and children irrespective of their status in the community. The services are provided by the Government. The private societies, which existed in the U.S.S.R. in former years, were in the course of time replaced by Government agencies. The plan of work is uniform; that is, the same method is used for the same kind of work by all institutions and agencies engaged in it; this is due to a central direction of the work by a national agency, the Commissariat of Public Health of the U.S.S.R. The services are free, on the principle of free medical care for all citizens, announced by the Constitution.

*Russian Soviet Federated Socialist Republic, the largest of the republics constituting the Union of the Soviet Socialist Republics; it occupies about nine-tenths of the Union's territory with about two-thirds of its population.

A further characteristic of the maternal and child-health work in the U.S.S.R. is the method of providing health services by district, each directed by a pediatrician. This was introduced in 1942 on the order of the Commissariat of Public Health. In this way each child is under the care of one pediatrician, except for specialists' services; this arrangement has increased the physician's sense of responsibility for the children under his care and has brought about a saving of his time; all this has resulted in improved services.

2. *Health and welfare services for mothers.* (See also section on health services in rural localities.)

Maternity clinics

Under regulations issued by the Commissariat of Public Health of the U.S.S.R. in 1938 and 1942, women receive at the maternity clinic prenatal care, care in the postnatal period, and treatment for pelvic diseases at any time.

Instruction in personal hygiene and infant care is given to the women individually at the clinic, at their places of employment, or at their homes. Informal talks, special lectures, and courses of instruction called "mothers' schools" are also provided.

Maternity homes

The Constitution of the U.S.S.R. provides for the establishment of an extensive system of maternity homes. These homes are built and equipped according to standards prescribed by the Commissariat of Public Health of the U.S.S.R. They are maintained at Government expense, with the exception of those on the collective farms.

The newborn children are separated from the mothers and placed in nurseries. The patients in the maternity homes are taught care of their own health and that of their children.

Rest homes

In large cities there are rest homes for expectant mothers and for mothers of young babies. The purpose of such homes is to enable the working woman to spend her authorized maternity leave under restful, hygienic conditions, so that she may regain her health. The women usually spend four weeks in these rest homes before childbirth and three weeks after.

3. *Health and welfare services for children*

Child-health centers in cities

At the child-health center preventive care and treatment in illness are provided for children under 4 years of age. Prior to 1943 the age limit was 3 years. Older children are cared for at the children's clinics. Pediatricians and nurses are employed at every child-health center, which as a rule serves a definite territory.

Consistent efforts are made by the center to bring under its control all newborn children in its territory. Information about births is obtained either from the maternity homes, or the registrar of vital statistics; sometimes the family itself reports the birth to the child-health center. It was reported in 1944 that in some child-health centers of Moscow, Leningrad, and other cities, 85 to 98 per cent of the newborn children in the district were under the care of a center. In some cities the percentage was much lower. Children are visited at their homes a few days after their mother's return from the maternity home, in recent years on the second or third day; in many cities, the first visits are made by physicians; in others, by nurses.

Ten to fourteen days after her discharge from the maternity home or hospital the mother is required to bring the child, if he is well, to the child-health center. If she fails to do so, a reminder is sent to her. The regulations require that the mother be given a copy of the "Booklet of the child's development," which she must read, keep, and present every time she attends a child-health center, day nursery, or hospital; she must also make certain that a notation is made in the booklet of each of her visits to the child-health center, day nursery, or hospital.

At the child-health center the physician, assisted by nurses, watches the child's development and state of health, and takes the necessary preventive measures, including immunization.

He notes his observations in the "record of development," which is kept at the center, and in the previously mentioned "Booklet of the child's development."

The public-health nurses attached to the urban child-health centers are required to visit the homes of the babies in the district. The first visit must be made not later than three days after the mother's discharge from the maternity home, and is followed by other visits at prescribed intervals. On these visits the public-health nurse is required to instruct the mother in the care of the child and of herself and to take measures for the improvement of the hygienic conditions in the home.

The reports of 26 child-health centers in the city of Moscow for 1943 showed that children less than 1 year of age were visited ten times in that year and older children twice. For other cities, the numbers varied.

The child-health center in a city is directed by a physician, who is appointed by the department of health of the city or of the city district. The department of health has general charge of the work of these centers. Sometimes a breast-milk station, or a station for the distribution of milk for children, is also a part of the center. A child-health center may be independent or combined with a maternity clinic. The child-health centers also have day beds during the summer for the treatment of children with acute diseases of the alimentary tract. Special "recovery playgrounds" are maintained at some child-health centers for children recovering from acute diseases and those suffering from rickets and from tuberculosis not requiring institutional treatment. The results of the work of these playgrounds are said to be very satisfactory.

Children's clinics

Children's clinics in cities and industrial settlements provide preventive and curative treatment for children 4 to 14 years of age. Children under 4 years of age are treated at child-health centers; those over 14 at the general clinics. This treatment includes periodic examination of school children and selection of those to be sent to recuperation homes, vacation camps, and similar institutions. In cities and industrial settlements in which no children's clinics are available, the work is done at children's divisions of general clinics; in rural localities at the rural medical stations. Children unable to come to the clinic receive medical care at their homes. Under an order of November 3, 1943, by the Commissar of Public Health of the U.S.S.R., the physician must visit a sick child at home on the same day he is called. Hospital care and treatment by specialists are also provided. Nurses employed at the clinic visit the children in their homes for the purpose of giving minor treatment, checking up whether the physicians' instructions are carried out, and instructing the mother in the care of the child.

Medical and dental care for school children

Instructions for the medical care of school children have been issued at various times by the public-health authorities. Directions for the improvement of this care were also included in the first, second, and third five-year plans for the economic reconstruction of Soviet Russia.

In 1943 the Commissar of Public Health of the U.S.S.R. called the attention of the public-health authorities to the unsatisfactory state of medical services for school children in some localities and ordered a reorganization of these services throughout the country. All children in kindergartens, schools, and institutions must now be examined twice annually and be given the necessary medical care, whether at clinics, hospitals, sanatoriums, or other institutions. In cities and industrial settlements one physician must be appointed for each 600 to 800 pre-school children (in 5 to 6 kindergartens) or 2,500 to 3,000 school children; also one nurse for each 200 to 300 children in 2 or 3 kindergartens, and 800 to 1,200 school children if they are in one school, and 700 to 800 if in 2 or 3 schools. The school physicians heretofore attached to the local public-health departments are to be transferred to the children's clinics together with the corresponding appropriations for their salaries. In the cities and towns where there are no children's clinics, the pre-school and school children will be examined and treated by other physicians on the designation of the local health authorities.

In rural localities the health work for pre-school and school children is to be done by the medical staffs of the rural clinics and rural medical stations under the direction of the pediatrician who has charge of the child-health services in the district of the province.

The Commissar ordered at the same time the appointment of a physician for each institution for children or residential school which the physician is required to visit at least three times a week in cities and at least twice a month in rural localities.

A graduate nurse must be attached to each children's institution or residential school for observing the children's health and taking preventive measures. To assure a sufficient number of nurses for this purpose the Commissar ordered the organization of a two-month course for the further training of 2,500 nurse-graduates of the Red Cross or Red Crescent courses. The public-health authorities were also directed to take measures for the health education of school children with the participation of teachers and parents. The responsibility for all this work was placed by the Commissar on the chief physicians of the local children's clinics or children's divisions of the general clinics.

Feeding of school children

Feeding of school children assumed great importance as the law on compulsory school attendance was gradually extended to all children. School feeding has come to be considered necessary to assure regular school attendance. Meals are served both in urban and rural schools.

Day nurseries

With the development of industry in the U.S.S.R., and the consequent demand for woman labor, the need for day nurseries became apparent, and the Government took steps for supplying this need. The problem of proper construction and equipment of day nurseries was considered in the preparation in 1932 of the second five-year plan for the economic reconstruction of the country, and standards for day nurseries were then prescribed.

The day nurseries are open to children between the ages of 2 months and 3 years. Older children go to kindergartens. Before admission to a day nursery the child must be examined by the pediatrician at the local child-health center. In order to prevent the spread of communicable diseases, the public-health nurse attached to the child-health center investigates the child's home. The day nurseries are divided into sections for children of different ages. A physician visits the day nursery to watch the children's health, to arrange for treatment in case of illness, and to assure the observance of the rules of sanitation and hygiene.

The day nurseries are maintained by the establishments to which they are attached—mostly by factories in cities and industrial settlements and by collective farms* in rural districts. A charge, varying with the parents' income, is made for the care of the children; a reduction is allowed for soldiers' children.

Following Germany's attack on the U.S.S.R. in 1941, when millions of women had to replace in industry the men called to the front, the day nursery came to be considered an institution of national importance. Larger funds became available for the construction of day nurseries, and in approximately one and one-half years their number (both in cities and on farms) grew 80 per cent in 35 provinces.

Among the changes necessitated by wartime conditions is the lengthening of the hours in the day nurseries; many are now open 12 to 14, even 24 hours a day, so that a child may remain there several days at a stretch. This has been found very helpful to employed mothers in case of the child's illness, or to mothers whose work takes them out of town part of the time. The Commissar of Public Health of the U.S.S.R. recently expressed himself in favor of increasing the facilities for round-the-clock care of ailing children not requiring hospitalization. Since 1941 there have been set up in many day nurseries separate sections for

*A collective farm is a cooperative organization in which the means of production and the farm buildings are the common property of the peasants constituting the collective farm; the land, which is the property of the State, is made available for the free and permanent use of the members of the collective farm. Each farmer's family is allowed to own the house in which it lives, a patch of land to cultivate for its own use, and some domestic animals. Part of the farm's crop is distributed among the collective farmers and part is sold to the Government; the proceeds from the sale are used for taxes and other expenses.

children suffering from chronic dysentery, or requiring isolation, quarantine, observation, or other attention. The children remain there for several weeks or months under medical supervision. As a result, the attendance of the registered children has improved, with a consequent decrease of loss of working time by the mothers.

At the end of 1943 it was estimated that about 45 per cent of children under 3 years of age in rural districts were cared for in permanent or seasonal day nurseries.

Institutions for children

In normal times institutions for children were organized and conducted in accordance with regulations issued in 1939 by the Commissariat of Public Health of the U.S.S.R. These institutions were intended for the following categories of children: (1) orphans who have no relatives able to care for them; (2) children of parents deprived of parental authority; (3) children of unknown parents; and (4) children whose mothers are employed as wet nurses in the institution. Children who had parents could be placed in an institution temporarily by special arrangement.

Children under 3 years of age were to be placed in separate institutions. For the purpose of better care the children were to be divided into groups of 15. Detailed rules were prescribed for the care of the children's health. Pediatricians examine all children and give treatment to those who are ill.

Recently the age limit for children in these institutions was raised to 4 years.

There are separate institutions for children between the ages of 3 or 4 and 8 years. Regulations prescribe medical and dental care for the children and facilities for their proper mental development and education. After a child reaches the age of 8 he is transferred to an institution for children of school age. There are also special institutions for physical or mental defectives and children in need of special care for other reasons. All these institutions are maintained by public funds and supervised by the local department of health.

Since the present war the importance of special protection for children in the U.S.S.R. has been stressed both by the Government and the people, particularly since the predominant majority of children have fathers or mothers in the armed forces. The devastation of the war created a need for large numbers of institutions for children. A Government decree issued in August, 1943, provides for the establishment of institutions for orphans and homeless children found in the territories liberated from the Germans prior to that time.

Foster-family care

Despite the great importance attached by the Government to institutions for children, foster-family placement has also been given a prominent place in the care of orphans and other homeless children.

4. Health services for mothers and children in rural localities

The Commissariat of Public Health of the U.S.S.R. has been giving particular attention to the health of the rural population. In addition to services similar to those in cities, such as child-health centers, clinics, hospitals, maternity homes, the rural districts have agencies not available in cities—intended to meet the particular needs of rural life.

The health services in the rural part of a province are supervised by the public-health inspector of the provincial department of health. Both the commissariat of public-health of each republic and the Commissariat of Public Health of the U.S.S.R. have special bureaus for the general supervision of all health work in rural localities.

Rural medical stations

Rural medical stations have been set up in the districts into which the provinces are divided. Each rural medical station serves its own territory; medical care of the population, preventive work, and sanitation are among its duties.

In cases in which the facilities of the rural medical station are insufficient to provide the necessary service, arrangements are made with a medical school, hospital, or other institution in the vicinity. Physicians from these institutions are sent to the rural station; sometimes ambulance airplanes, and medical and dental mobile clinics are sent also.

Many of these stations are equipped with clinical-diagnostic laboratories and medical libraries sent to them by the Commissariat of Public Health of the U.S.S.R.

The rural medical station is directed by a physician under the immediate supervision of the department of health of the provincial district in which it is situated. The provincial district also supplies the funds for the maintenance of the station.

Feldsher's stations

A feldsher's station is directed by a feldsher, who may be briefly described as a physician's assistant. The feldsher is a graduate of a special school with a three-year course limited to certain medical subjects; his professional field is definitely restricted. He is allowed to give first aid and treatment in minor illnesses, either at his office or at the patient's home, within the limitations imposed on his activities. More serious cases must be referred by him to a physician in the district. The feldsher inspects health conditions in the day nurseries, kindergartens, schools, and vacation camps in his district, and examines the children in these institutions.

In the localities lacking stationary physicians, the feldsher watches the well children under the general supervision of the physician in charge of the rural medical station, who visits these localities at intervals. The feldsher inspects the well children between the physician's examinations and selects for the physician's attention those who do not develop normally. He must be present at the examinations by the physician.

The feminine counterpart of a feldsher is a feldsheritsa. Large numbers of both are trained and employed in the U.S.S.R.

Sanatoriums for children on collective farms

A new kind of health agency in rural districts is the special sanatorium for children on collective farms. Such sanatoriums were set up for the first time in 1944, in several localities at the suggestion of rural physicians, who had found that many farmers' children suffering from rickets, malnutrition, and other conditions did not respond to treatment while staying at home. The children at these sanatoriums are treated by the physician stationed in the locality who is aided by graduate nurses. The sanatoriums, usually accommodating up to 40 patients, are maintained jointly by the collective farms and the official local commissions for the care of soldiers' families.

Maternity clinics in rural districts

Maternity clinics are available for expectant mothers in rural districts. Midwives or nurses stationed in the locality visit the homes of the women attending the clinics.

C. Other activities connected with services for mothers and children

1. Training of personnel

Medical training is given at the medical institute (equivalent to school of medicine in the United States). For admission to such an institute, graduation from a 10-year combined grammar-school and high-school course is required.

Some of the medical institutes have three departments each training specialists in the particular field: (1) general medical course; (2) sanitation and hygiene; (3) pediatrics. In 1941, 26 of the 72 medical institutes in the country had pediatric departments with an enrollment of 18,000 students. Pediatrics is also taught in the other medical institutes. The course in the institutes covers 5 years; for a brief period during the war of 1941-1945, it was shortened. Beginning with September, 1945, new subjects will be added, and the course will be lengthened to 6 years.

Graduates of medical institutes receive the title of physician. Those who do very good undergraduate work are permitted to study 3 more years for the degree of candidate of medical sciences. After several years of further study one obtains the highest degree, that of doctor of medical sciences. Physicians stationed in rural localities are required every three years to take not less than three months of graduate work; city physicians every five years. During their graduate study the physicians are paid their salaries in full as well as their traveling and living expenses.

Facilities for graduate study in pediatrics are available at the "scientific research institutes for the protection of mothers and infants," some of which have been renamed in recent years "pediatric medical institutes" or "research institutes of pediatrics."

In 1943 the Commissar of Public Health of the U.S.S.R. ordered the organization of refresher course for pediatricians. Also about the same time correspondence courses for graduate pediatricians were organized in Moscow. The facilities were calculated for 1,000 persons, but a larger number applied, mostly from rural localities. M. D. Kovriguina, Vice-Commissar of Public Health of the U.S.S.R. in charge of child-health services, said that much work was done in 1943 for improving the qualifications of physicians and other personnel in the child-health services, but the improvement was still insufficient.

The establishment of refresher courses for public-health personnel was ordered in 1938 by the Commissar of Public Health of the U.S.S.R. as follows: (1) One-year courses on the organization of public health for directors of city departments of health who had received no medical education and had been in their positions three years; (2) three-month courses for the vice-commissars of public health of the republics and directors and assistant directors of the provincial departments of health; (3) three-month courses for persons in responsible positions in the different branches of public health, such as child-health work, health education and medical care for the general population; and (4) three-month courses for physicians in charge of hospitals and out-patient clinics and for directors of departments of health in city districts. The commissars of public health of the constituent republics were made responsible for the enforcement of this decree.

2. Participation of citizens' groups in the health work for mothers and children

The agencies engaged in health or welfare work for mothers and children in the U.S.S.R. are often aided by citizens' committees or councils. The composition and functions of these groups vary according to the nature of the agency or institution to which they are attached.

The Commissar of Public Health of the U.S.S.R. ordered in 1939 the setting up of cooperating councils in connection with all out-patient clinics, hospitals, child-health centers, and other institutions for the medical treatment or preventive care of children or adults. Under the guidance of the director of the particular institution, the council is to examine the plans for the institution's work, to help in the preventive work and health education, and to decide on measures for improving the quality of the institution's services. The cooperating council is appointed by the local department of health and consists of the director of the institution, who serves as chairman, and of representatives of the institution's staff, the local department of health, the Red Cross, trade unions, and other citizens' groups. The number of members may vary between 15 and 40. The council is to meet at least once a month. The council's decisions must be put into effect by the director of the institution. In case of difference of opinion between the director and the council, the matter is referred to the local public-health authorities.

APPENDIX

1. Labor and social-insurance legislation as it applies to mothers and children

Industrial employment is regulated by the Labor Code. The minimum age prescribed by the Code for employment is 16 years, with exemptions permitted at the age of 14 years. However, employment at 14 years of age has become frequent since 1941 because of wartime shortage of man power.

Maternity leave is regulated by the law of July 8, 1944, on greater protection of the family. By law, nursing mothers are allowed time for nursing their children. This time is included in the hours of work. According to statements in Russian sources the protective legislation for working mothers has remained in force during the war of 1941-1945.

Social insurance is required of all persons, whether employed by the Government, co-operatives, or private organizations.

Under social insurance the workers are entitled to the following benefits:

1. Medical care;
2. Cash payments for time lost because of illness, injury, quarantine, pregnancy, childbirth, or the necessity of caring for an ill member of the family;

3. Childbirth and nursing benefits;
4. Pensions in case of permanent invalidity or old age;
5. Funeral benefits; benefits to dependents of a deceased breadwinner of the family.

Unemployment benefits were discontinued in 1930 because of the liquidation of unemployment.

To meet the cost of social insurance, the establishments or individuals employing workers are required to pay into the insurance fund a specified percentage of their payroll. The employers are prohibited by law from deducting these payments from the workers' wages or from otherwise charging them to the workers. No payments are required from the workers.

2. *School-attendance legislation*

School attendance, which was voluntary in Russia under the Czars, was made compulsory soon after the overthrow of the Czarist regime in 1917. Because of the immensity of the problem and the insufficiency of facilities needed to provide schooling for all children of school age, the Government decided to introduce compulsory school attendance gradually, making it applicable at first to the older children and extending it by degrees to the younger-age groups, first in cities and later in rural localities. In September, 1944, the application of the compulsory-school-attendance law was extended to include children 7 years of age; previously 8 years was the age for entering school.

3. *Law of July 8, 1944, on greater protection of the family*

The law of July 8, 1944, on greater protection of the family, continues a trend manifested in the law of June 27, 1936. The 1944 law provides for similar types of grants: single payments on the birth of a child and allowances for a specified period of his life. The first single payment is 400 rubles* upon the birth of the third child; the amount of this payment increases gradually to 5,000 rubles, payable upon the birth of the eleventh child and of every subsequent one.

The allowances are paid monthly for 4 years from the child's first birthday to his fifth. They begin at 80 rubles a month for the fourth child and increase gradually to 300 rubles a month for the eleventh and for every subsequent child.

The period of maternity leave for women in factories and offices—during which, under the labor and social-insurance code, their employment is prohibited and their wages paid in full—has now been extended to 35 days before childbirth and 42 days afterward.

The special taxation of unmarried persons and those married but childless, which was introduced under a decree of November 21, 1941, is now extended to married persons with fewer than three children. The tax applies to men from 20 to 50 years of age and to women from 20 to 45. For a person subject to general-income tax this special tax will be 6 per cent of his income if he is childless; 1 per cent if he has one child.

The mother of a child born out of wedlock is deprived of the right to seek court action for the establishment of paternity and for obtaining support from the child's father; also, she is required to give her own surname to the child.

Stringent rules regarding divorce are prescribed in the new law, which requires court action according to a definite procedure. Under the law of 1936 the only requirement was that both parties appear before the local registrar of vital statistics.

The law of 1936 introduced, as a possible deterrent to divorce, a fee of 50 rubles for the first divorce, 150 rubles for the second, and 300 for the third and any subsequent one. Now a payment of 100 rubles is required at the time of filing the petition; and the fee for the divorce itself, payable by one of the parties or jointly by both, varies, at the discretion of the court from 500 to 2,000 rubles, a price considered prohibitive for the average person.

4. *Institutes of research in pediatrics, obstetrics, and gynecology*

The institutes of pediatric research are centers for the study of problems relating to the prevention of disease among children, improvement of diagnosis, reduction of mortality,

*The nominal foreign-exchange value of a ruble was 20 cents before 1940; its present value is not quoted.

and development of other methods of safeguarding child health. To this end investigations are made at the institutes of the more prevalent children's diseases. Statistics of children's morbidity and mortality are analyzed; standards are formulated for children's hospitals, clinics, and health centers, and for other child-health and welfare services; advice and information are given to various institutions and agencies; and popular literature is published. There are also institutes of obstetrics and gynecology.

Formerly the institutes of pediatric research and those of obstetrics and gynecology were combined into "institutes for the protection of mothers and infants." In some localities such institutes are still in existence.

All these institutes collaborate with the various health agencies and give them systematic advice in their work. The institutes also have facilities for training pediatricians, obstetrician-gynecologists, and nurses for the health services. The extent of the institutes' activities varies considerably and depends, among other things, on the territory served by the individual institute. A few of the institutes are federal and serve the entire country; others belong to the republics constituting the U.S.S.R.; the remainder are provincial or municipal. They are all under the general supervision of the Commissariat of the Public Health of the U.S.S.R.

Twenty-three institutes were operating in the U.S.S.R. before 1941. Several of them stopped their work when their buildings and equipment were destroyed by the invading Germans in 1941 and 1942; however, some were rebuilt as the territories were gradually reconquered by the Russians.

One of the most important institutes because of the large scale of its research and teaching activities is the Leningrad State Pediatric Medical Institute, established in 1925 under the name of "Leningrad Scientific Institute for the Protection of Mothers and Infants"; in 1935 it was given its present name.

Some of the Institute's functions are as follows:

1. Theoretical and practical study of the anatomy, physiology, psychology, hygiene, dietetics, and pathology of the infant and young child.
2. Study of various forms of child-health services and decision on measures for their improvement.
3. Information and advice to public and private agencies and to individuals on the subjects relating to the Institute's work.
4. Training of physicians and nurses for child-health services.
5. Preventive and curative treatment of children.

For the study of the physiology of the well child the Institute has a separate department with accommodations for more than 100 newborn children, babies under 1 year of age, and older children. In another department are studied the diseases peculiar to infancy and early childhood, also venereal diseases, diseases of the nerves, and others; there is also a surgical clinic. In a dispensary treatment is given to children for various diseases, including tuberculosis, diseases of the skin, eye, ear, nose, and throat, and others; dental care is also provided.

The Institute has a department of physiotherapy, an x-ray department, a milk and dietetic station, and numerous laboratories and shops for the preparation of technical instruments; there are also exhibits on child care, and a library with a reading hall.

Another phase of the Institute's work is the training it provides for physicians and nurses who intend to enter the child-health services. For this purpose the Institute has departments in which instruction is provided in such subjects as health services for infants and children; physiology, hygiene, and dietetics of infancy; pathology of infancy; surgical pediatrics; and venereal disease. There is also a school for the training of nurses. Numerous reports have been published by the Institute.

News and Notes

Many Fellows are not familiar with the Tumor Registry Committee of the Academy. Dr. Harold W. Dargeon, 1095 Park Avenue, New York 28, is Chairman and associated with him are Drs. Herbert F. Jackson and Hayes Martin of New York.

Dr. Willis J. Potts, who has been a member of the surgical staff of the Children's Memorial Hospital in Chicago since 1931, will become head of the department of surgery on April 1, 1946. Dr. Albert H. Montgomery, who was formerly in charge, will remain as consulting surgeon.

The Pediatrician and the War

The following Fellows have been released from service:

Dr. Louis Appel, Flushing, N. Y.
Dr. Barnett P. Briggs, Little Rock, Ark.
Dr. George W. Caldwell, New York, N. Y.
Dr. Nathan H. Einhorn, Yeadon, Pa.
Dr. R. Bruce Eldredge, Los Angeles, Calif.
Dr. Herbert L. Elias, Rockville Center, L. I., N. Y.
Dr. Harry H. Gordon, New York, N. Y.
Dr. Raymond F. Grisson, Oak Park, Ill.
Dr. Wesley R. Heard, Pasadena, Calif.
Dr. Richard C. Hiestand, Springfield, Ohio
Dr. Alvin H. Jacobs, San Francisco, Calif.
Dr. Robert M. Keagy, Altoona, Pa.
Dr. George N. Leonard, Miami Beach, Fla.
Dr. Albert U. Peacock, Hartford, Conn.
Dr. Samuel X. Radbill, Philadelphia, Pa.
Dr. Thomas F. Reilly, Springfield, Mass.
Dr. W. Pierre Robert, Beaumont, Texas
Dr. Hulda E. Thelander, San Francisco, Calif.
Dr. Walter M. Whitaker, Quincy, Ill.
Dr. Byron P. York, Houston, Texas

The following promotions have been reported to the JOURNAL:

Major Harry H. Gordon to Lieutenant Colonel
Lieutenant Commander Milton Kurzrok to Commander
Lieutenant Commander Thomas F. Reilly to Commander
Major Samuel P. Wainwright to Lieutenant Colonel

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Original Communications

THE THICKNESS OF THE SKIN AND SUBCUTANEOUS TISSUE BY AGE AND SEX IN CHILDHOOD

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IT HAS been common practice to note the amount or thickness of the soft tissues overlying certain muscle groups as a part of the routine physical examination of infants and children. The usual procedure has been to select a fold of these tissues in a part which is freely movable, as over the biceps or recti, and assign a rating subjectively, but some physicians have measured this thickness with a ruler, and Franzen¹ devised a special spring caliper to determine it under constant pressure. The thickness of these tissues has received attention as an indication of nutritional state for the obvious reason that the subcutaneous tissue is a repository for the storage of fat and hence reflects any large accumulations or withdrawals of fat in the body. The accumulation or loss of water in this tissue may also account for rapid change in its thickness, but characteristic differences in tissue quality are usually associated with edema or dehydration so that the clinician can recognize when this measurement is grossly distorted by changes in the storage of water.

The subcutaneous tissue varies characteristically in thickness between individuals of different body types, and this variation has much to do with a child's customary position in the weight range and with how closely his weight will approximate the average weight for height and age. The range of difference in this respect between individuals of the same age and in apparent good health is proportionately greater than for most physical attributes. Using Sheldon's² classification of body types, a person predominantly endomorphic in type characteristically will have a heavy panniculus adiposus, and hence a thick fold of subcutaneous tissue, whereas an ectomorphic individual will tend to have a light or thin one. These persistent individual characteristics must be taken into account in assessing physical or nutritional status. Associated with differences in physical type undoubtedly are differences in the consumption and utilization of food and in the amount of physical or the rate of physiologic activities, but to some extent these differences may be considered constitutional.

From the Department of Maternal and Child Health, Harvard School of Public Health.
The studies being reported were made possible during the earlier years by a grant from the General Education Board. During the past three years they have been supported by the James Foundation.

What would represent a normal continuing and satisfactory amount of subcutaneous tissue for one individual might represent gross malnutrition and loss of body substance for another. However, the multiple correlation of five skeletal dimensions with amount of subcutaneous tissue was shown by Franzen¹ to be of a considerably lower order than with amount of muscle, and much lower than with weight. Since weight is primarily a characteristic of body dimensions and can be predicted fairly accurately from a battery of them, and since amount of subcutaneous tissue is much more independent of skeletal dimensions, Franzen concluded that objective determination of the thickness of subcutaneous tissue offers a fuller understanding of nutritional state than does body weight.

Sex and age differences in respect to the thickness of the subcutaneous tissue also have been appreciated to some extent. Franzen called attention to the greater average thickness of this tissue and the greater variability in this respect among girls than among boys of school age. The newborn infant, the preschool child, the young adult, and the elderly person are generally recognized to have less fat in their soft tissues than are the infant 3 to 9 months of age, the adolescent, and the adult of middle age. There are further differences with regard to age in the characteristic locations in which fat is most readily accumulated, but these are of less clinical importance than the recognition of periods of ready accumulation alternating with periods of normal diminution in these stores.

It is clear that valid judgment as to the significance of the amount of skin and subcutaneous tissue in any individual can be made only when age, sex, build, and other contributory factors are taken into account. The evaluation of the thickness of these tissues should continue to receive the attention of physicians in assessing physical status, but this should be done in as objective a manner as possible, and further information is required regarding normal occurrences under the varying conditions referred to.

It is unnecessary to review here the literature on the use and interpretation of direct measurements of skin and subcutaneous tissue because of the excellent studies and discussions of this subject by McCloy³ published in 1936 and 1938, and the more recent review by Reynolds⁴ in connection with studies referred to subsequently. Since McCloy's thorough evaluation of direct measurements, roentgenograms have been used to afford indirect measurements of the soft tissues. Stuart, Hill, and Shaw⁵ described a method, applicable to children up to 6 years of age, based upon anteroposterior roentgenograms of the tibial shaft sector of the leg, from which they obtained values for the areas as well as the breadths of the shadows of bone, muscle, and skin and subcutaneous tissues. Norms were presented for these measurements as well as individual case studies. Stuart and Hill⁶ in a later publication described a slightly modified technique for use with older children and norms were added for the ages from 6 to 10 years. This method has been used to advantage in several studies of growth and nutrition.^{7, 8, 9} Reynolds⁴ described a somewhat different technique for using roentgenograms for this purpose, the principal difference being that the film cassette was placed behind the calf of the leg with the child standing, whereas Stuart

and Hill⁶ had placed the cassette below the calf with the child recumbent. Reynolds presented norms for actual and relative breadths of the three tissue shadows in the leg for ages from 6½ through 11½ years. His values for breadth of subcutaneous tissue were in very close agreement with those previously published by the other authors.⁶

In connection with the broader studies of growth and development being conducted by the Department of Maternal and Child Health of the Harvard School of Public Health,¹⁰ the special studies of roentgenograms of the leg have now been carried out on a considerable number of children through their thirteenth birthdays. The two earlier publications dealing with these studies have been referred to,^{5, 6} and the techniques used are briefly summarized here-with.† The measurements of the breadth of skin and subcutaneous tissue as obtained in these investigations provide the basis for this report. This measurement, as indicated in the footnote, is the width of the inner and outer shadows cast by the soft tissues overlying the muscles at the greatest breadth of the calf. Although both skin and subcutaneous tissue are included, the term "subcutaneous tissue" will be used henceforth in the text when referring to this measurement.

The measurements of subcutaneous tissue thus derived are presented in Tables I and II for each sex, by age, as percentiles and as means with standard deviations. Certain percentiles are also plotted for the two sexes in Fig. 1. The 50th percentiles in this figure show the marked differences in the average amount of this tissue in infancy as contrasted to childhood, and between girls and boys. The latter difference is slight or questionable in infancy but becomes consistently of more marked degree after two years of age. The 10th and 90th percentiles, including between them 80 per cent of each sex in the series, indicate the extent of variability at different ages.

Fig. 1 shows clearly that the subcutaneous tissue does not increase progressively with age but rather increases and diminishes in cycles, and that girls

*Reynolds studied children of school age and found the standing position satisfactory for the measurement of tissue breadths. The studies of Stuart and his co-workers started with birth, and the recumbent position was essential during infancy. At the age when a child will stand satisfactorily, he will also usually relax when laid on a table, and his leg can then be placed in the proper position without force, and without securing his active cooperation. In following physical attributes throughout the growth period it is often necessary to modify techniques to some extent at different age periods, but it is desirable to have any set of data as comparable as possible at all ages. In the larger project of which the study being reported is a part, the same children have been followed periodically at prescribed age intervals from birth, the oldest children now being 17 years of age. Although both recumbent length and standing height are taken, the former measurement is preferred and used in all case studies. Since use of the recumbent position in taking roentgenograms of the leg has proved satisfactory at all ages, this position has been continued. However, due care must be taken to follow the relatively simple rules prescribed to avoid distortion of shadows.

†The child lies flat on the back with the right leg fully extended at the knee, with the entire leg over the film cassette and with the foot perpendicular to the table. In order to secure the complete extension and near parallelism between the leg and the cassette, and the correct position of the foot, it is usually necessary with the infant and often with the young child for an assistant to exert moderate pressure over the lower thigh with one hand while supporting the foot with the other. Forceful pressure over the thigh is avoided in order not to distort the calf by compressing it against the cassette. The older child usually adopts the correct position as directed and requires no holding.

The x-ray tube is centered over the broadest part of the calf at thirty-six inches distance from the film for children up to 6 years of age, and at seventy-two inches for children 6 years and older. The exposure must be such as will allow clear visualization of the outlines of skin, muscle, and bone.

The greatest breadth of calf is determined arbitrarily by measuring the length of the tibial shaft and taking a point three-tenths of this length from the upper end of the shaft. A transverse line drawn through this point was found to give regularly as great a breadth of calf as muscle. The former measurement minus the latter is the measurement of skin and subcutaneous tissue used in this report, usually referred to simply as subcutaneous tissue.

TABLE I. BREADTH OF SKIN AND SUBCUTANEOUS TISSUE (IN MILLIMETERS) OF BOYS
DISTRIBUTIONS FOR MEASUREMENTS FROM ANTEROPOSTERIOR ROENTGENOGRAMS

AGE (YR.)	PERCENTILES					NO. OF CASES	MEAN	S. D.*
	10	25	50	75	90			
<i>A. Three-Foot Tube Distance</i>								
¼	12	13	15	18	20	66	15	3.3
½	14	17	20	22	24	64	19	3.4
¾	16	18	21	24	26	59	21	4.1
1	15	17	19	22	24	78	19	3.4
1½	14	15	17	19	21	57	17	2.7
2	13	14	16	18	19	74	16	2.8
2½	12	13	14	16	18	66	14	2.3
3	10	12	14	16	18	80	14	2.7
3½	10	12	13	15	17	60	13	2.5
4	10	11	13	14	16	71	13	2.8
4½	10	11	12	14	16	52	12	2.3
5	9	10	12	13	16	71	12	2.6
5½	9	10	11	13	15	54	12	2.6
6	8	10	11	13	16	53	11	3.0
<i>B. Six-Foot Tube Distance</i>								
6	8	10	11	12	14	59	10	2.0
7	8	9	11	12	14	73	10	3.0
8	8	9	11	12	14	64	11	3.0
9	8	8	10	12	14	55	11	3.6
10	8	8	10	12	14	35	10	2.4
11	8	8	12	13	15	25	11	3.1
12	8	9	11	16	19	20	12	3.8
13	8	9	12	16	22	29	14	7.0

*Standard deviation.

TABLE II. BREADTH OF SKIN AND SUBCUTANEOUS TISSUE (IN MILLIMETERS) OF GIRLS
DISTRIBUTIONS FOR MEASUREMENTS FROM ANTEROPOSTERIOR ROENTGENOGRAMS

AGE (YR.)	PERCENTILES					NO. OF CASES	MEAN	S. D. *
	10	25	50	75	90			
<i>A. Three-Foot Tube Distance</i>								
¼	13	15	17	19	20	68	17	2.5
½	16	18	20	22	25	63	19	3.2
¾	17	19	21	23	26	59	21	3.2
1	16	18	20	23	25	74	19	3.2
1½	15	16	17	19	22	60	18	2.8
2	14	15	17	19	21	79	17	2.8
2½	13	15	16	19	21	62	17	2.8
3	13	14	15	18	20	79	16	2.7
3½	12	13	15	17	20	54	15	2.7
4	12	13	15	17	19	72	15	2.6
4½	11	12	14	17	18	60	14	2.7
5	12	13	14	16	18	67	14	2.5
5½	11	12	13	15	17	53	14	2.6
6	11	12	13	15	16	42	14	2.2
<i>B. Six-Foot Tube Distance</i>								
6	10	12	13	16	17	58	13	2.5
7	10	12	13	16	17	63	13	2.8
8	11	12	13	16	18	51	14	2.7
9	11	12	13	16	19	55	14	3.4
10	11	12	14	17	19	42	15	3.5
11	11	12	14	17	19	27	14	3.1
12	13	14	16	18	21	20	16	3.2
13	13	15	17	20	24	19	18	4.2

*Standard deviation.

BREADTH OF SKIN AND SUBCUTANEOUS TISSUE IN LEG

(BREADTH OF CALF LESS BREADTH OF MUSCLE FROM A-P ROENTGENOGRAMS)

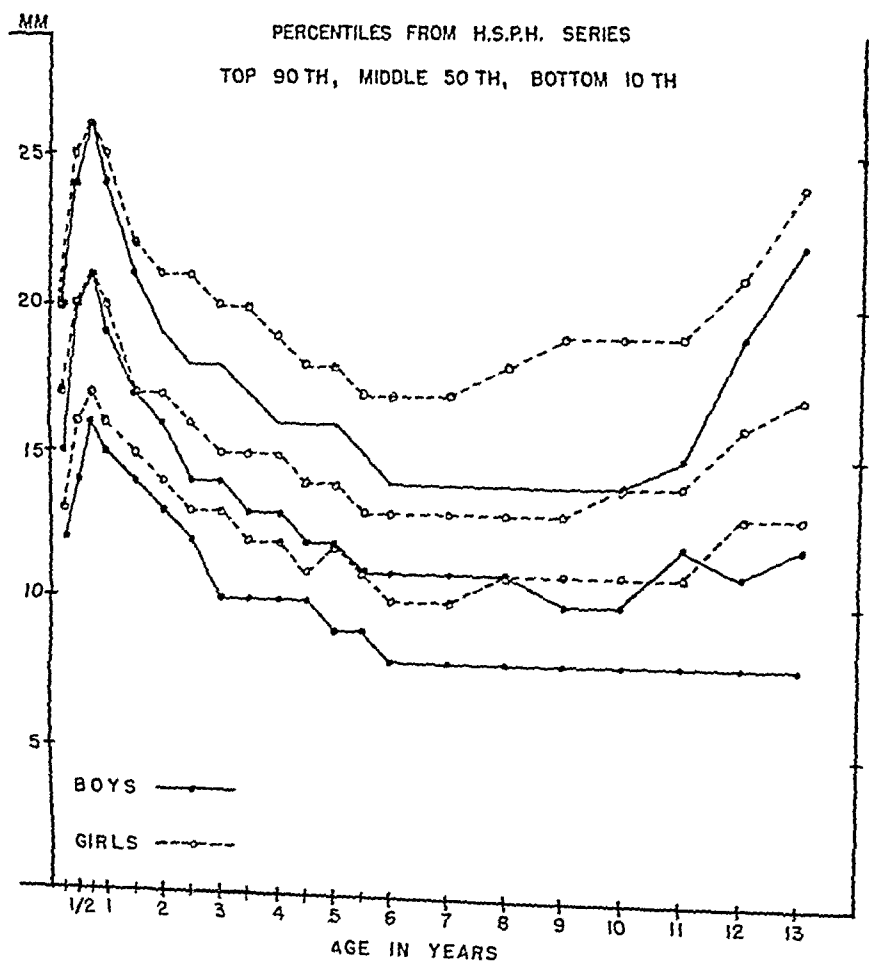


Fig 1—The graphs in this figure are based upon the norms presented in Tables I and II. They show the characteristic differences in amount of subcutaneous tissue by age and by sex. They also show the wide dispersion of measurements at each age, 10 per cent of each group being excluded above and below the limiting percentiles given. The curves are not plotted from birth to 2 months and figures are not given for birth in the tables because the roentgenograms taken at that age so frequently showed faulty position. However, the good films indicate that the thickness of subcutaneous tissue at birth is on the average for both sexes about 6.0 mm. Thus, this tissue approximately doubles in thickness during the first three months, and the rise in the graph if plotted would be steeper prior to 3 months than between 3 and 6 months of age.

tend from early childhood to have a thicker panniculus than boys. It shows the necessity for using different criteria in evaluating the physical or nutritional status of boys and girls on the basis of amount of subcutaneous tissue.

Having established a normal expectancy for age and sex in respect to amount of subcutaneous tissue, it is of interest to know how consistent individuals are in following the customary pattern. Can an individual found high or low in the distribution at one age be expected to remain in the same relative position, from year to year throughout childhood, as is customary with skeletal

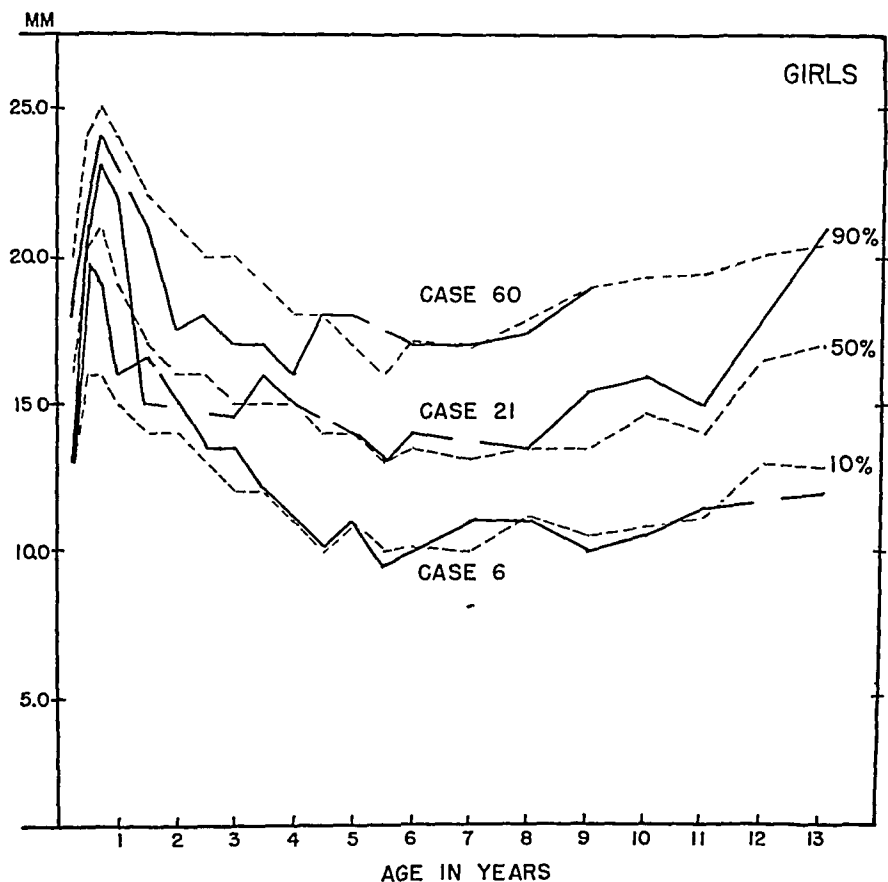


Fig. 2.—This figure shows the curves for amount of skin and subcutaneous tissue of three girls (solid lines) plotted against the 10th, 50th, and 90th percentiles for girls (broken lines). The norms used in this and subsequent figures differ slightly from those presented in Fig. 1 because the latter represents a more recent revision of our data.

Case 6. This girl had a small amount of subcutaneous tissue at all ages but was relatively heavy for herself from 6 months to 2 years. The socioeconomic circumstances of this child's family were continually unfavorable during her childhood, and her position in this distribution may have been influenced thereby.

Case 21. This girl had an average amount of subcutaneous tissue throughout childhood but accumulated excess fat during infancy and adolescence.

Case 60. This girl usually had a thick subcutaneous tissue but became relatively thin for a period from 2 through 4 years of age.

measurements? The data at hand are peculiarly well suited to throw light on this question since so many determinations have been made on the same individuals over such a large portion of the growth period.

Most of the individuals in the series on which these norms are based have conformed to the pattern of change with age as set forth, and, whether fat or thin, have been more or less so at different ages in accordance with this pattern. Fig. 2 shows the curves for three girls, chosen to represent what might be called 10th percentile, 50th percentile, and 90th percentile girls, plotted against the norms for these percentiles. It will be seen that the curves for these individuals follow those for the total series more closely in mid-childhood than they do in infancy or as adolescence approaches. This is in agreement with findings in other aspects of growth, in that the individual tends to be less con-

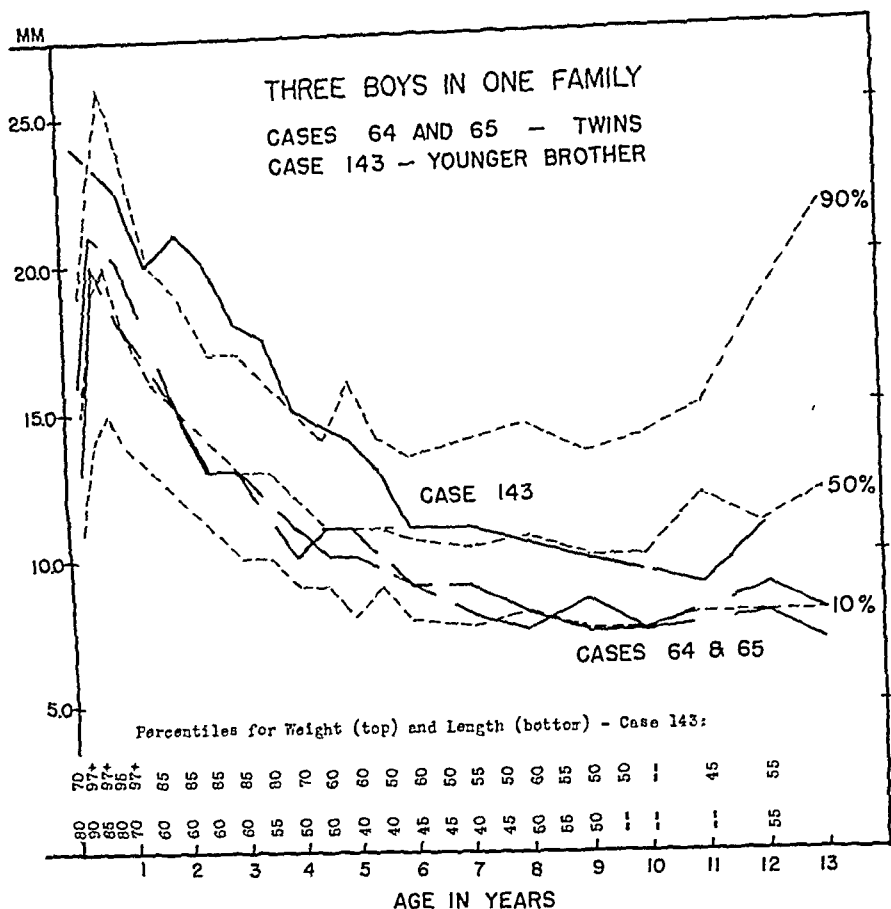


Fig. 3.—The curves of three brothers are presented in this figure because they show a similar change in position respecting the amount of subcutaneous tissue between infancy and six years.

Case 143. This boy showed an extreme amount of this tissue at 3 months of age but had reached an average amount at 8 years and remained average thereafter. His position in the range for length fell somewhat during the former period and his weight during infancy suggests real obesity.

Cases 64 and 65. The older twin brothers of this boy were strikingly alike at all ages and consistently had less subcutaneous tissue than he did. However, the curves of all three children show a similar trend to a lower position in childhood than that held in infancy. Because of this similarity in the behavior of these three brothers, it is assumed that the unusual feature of their growth was dependent upon constitutional or familial factors.

sistent in his position in the range and more readily drifts out of his appropriate channel during the periods of rapid growth than during the intervening period of more moderate growth.

A few children in this series have deviated very markedly from the expected course in respect to the amount of subcutaneous tissue in the calf of the leg at successive ages. In a number of cases there has been a gradual drift from one position in the range to a higher or lower one and the new position has then been maintained at least for a considerable period of time. Satisfactory explanations for these changes have not always been found in the records of food consumption, activity, or illness, and they appear to represent more fundamental variations of individual or family growth patterns. Some of these deflections may be explained, as in other body measurements, by differences between the

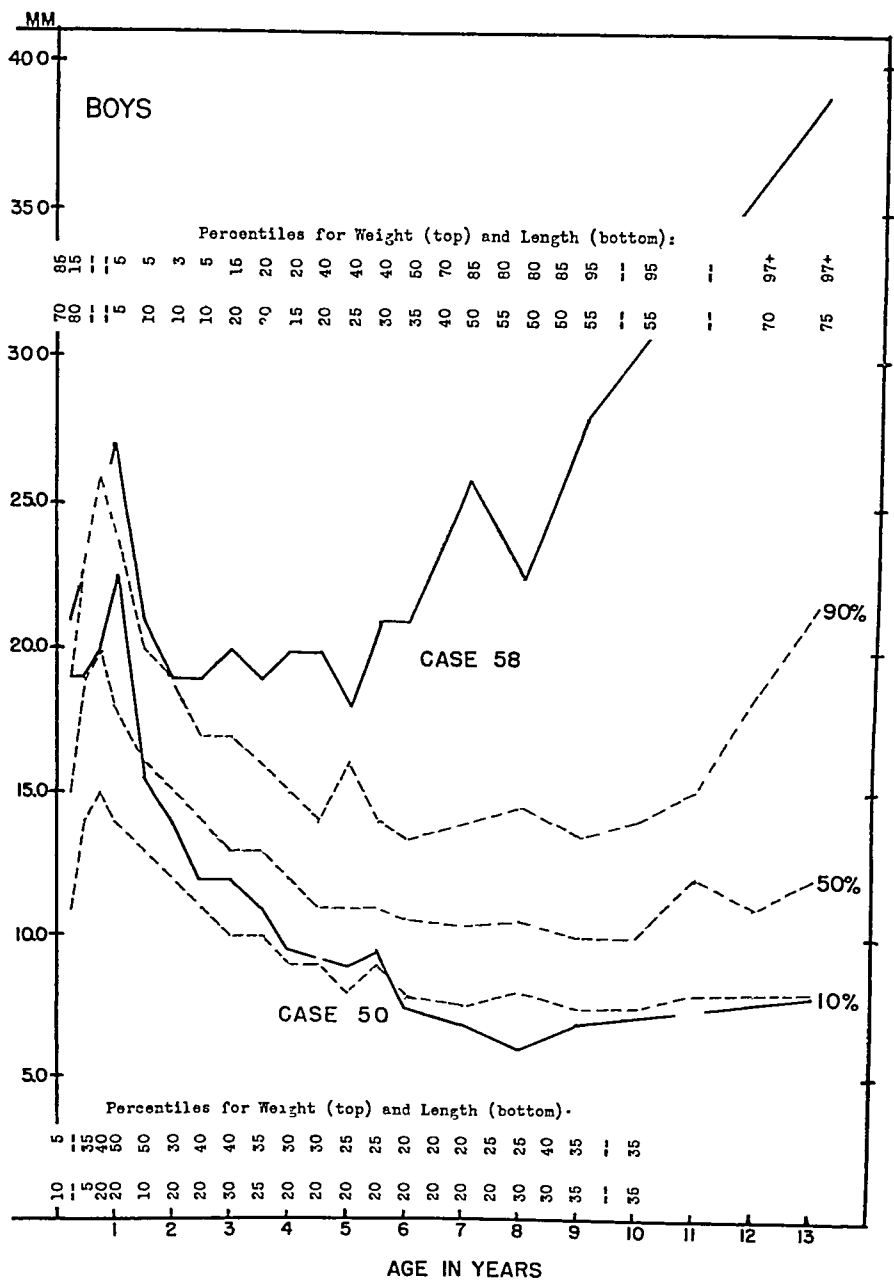


Fig 4—This figure presents two contrasting cases in respect to amount of subcutaneous tissue, which did not differ strikingly in this respect until after the first year.

Case 58. This child was temporarily retarded in growth during infancy as shown in the percentiles for height and weight at the top of the figure. This retardation was gradually overcome and he climbed to his initial position for height by his thirteenth year. Concurrently with his retardation he lost subcutaneous tissue and with his acceleration he gained in this respect but at all ages he was obese and he became extreme in this respect as an older child. At 13 years of age his weight was 6.4 kg above the 95th percentile. His secondary sex characteristics were developed to an average degree at this age, and his osseous development was never unusual.

(Cont d on opposite page)

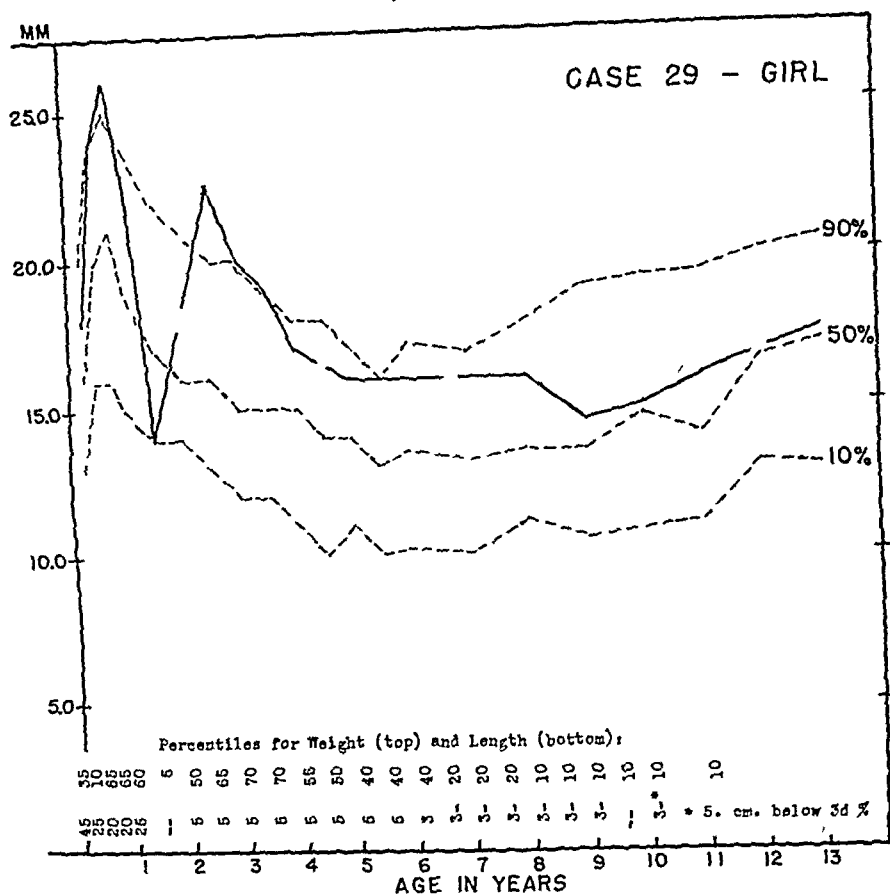


Fig. 5.—Case 29. This case is presented because of two abnormalities which were probably to a large extent unrelated. The girl had a short course of celiac disease first recognized at 18 months of age and causing few symptoms after 2 years. In addition, she was stunted in linear growth in the growth of her lower extremities. The retardation was progressive. At age 5 she was by a considerable amount the shortest girl in our series. Her disease remained ample in amount at all ages except at the time of her celiac disease. Changes in body weight reflected the changes in body size and in amount of soft tissue. Except for the period of restriction while under treatment for celiac disease, this child's diet was considered good up to 5 years of age but only fair or poor for all periods thereafter. The principal deficiencies were in protein and calories.

developmental age and the chronological age of the individual at the time. For example, a girl whose tissue measurement rises steadily between 8 and 10 years of age, when the customary curve is quite flat, may simply be precociously manifesting the rise which commonly accompanies the adolescent acceleration of growth.

In addition to these exceptional trends away from the anticipated course more commonly followed, many children have presented rather marked deviations

(Legend cont'd.)

Case 50. This child was always a more nearly normal individual, being somewhat short but having a satisfactory weight for height and for a short period during infancy being rather heavy, as shown by the percentiles at the bottom of the figure. At 13 years the measurement of the breadth of subcutaneous tissue in Case 50 was 3.9 cm., whereas that in Case 58 was 0.8 cm., a difference of nearly 500 per cent. The dietary histories of these boys did not show differences in customary calorie intakes adequate to explain this finding on a dietary basis. There are many other aspects of the growth and development of Case 58 which are of interest, but outside the scope of this paper. It is planned to present his case more fully in another connection, but his chart is shown here simply as an instance of gross deviation from the normal range for this measurement.

for short periods, remaining at other times in much the same position within the range. Some deviations in the curves are quite clearly exaggerations of normal trends, as, for examples, temporary obesity between 6 and 9 months of age, or excessive loss of soft tissue between 3 and 5 years of age. However, others appear to be related to nutritional factors, disease, or possibly to habits or environment.

Examples of unusual growth patterns, representing some of the types referred to, are presented in Figs. 3, 4, and 5. In the legends to these figures, brief summaries of pertinent clinical data are given to show the most striking relationships, but no attempt has been made to study or present exhaustively all possibly related information available in the records. The purpose here is not to establish the causes for individual variations but merely to call attention to the types which have been recognized. It is proposed, in subsequent reports, to correlate amount of subcutaneous tissue with dietary and other factors and to present more nearly complete case histories.

In the accompanying figures the percentiles for body length and weight by age for a few cases are given in order to show to what extent position in the ranges for these measurements has varied at the times of the unusual trends in the amount of subcutaneous tissue. In a previous publication⁵ one of us presented graphs for a number of children which allowed comparisons between the status held and progress made in weight, length, breadth of pelvis, and amounts of bone, muscle, and subcutaneous tissue in the calf. The latter measurements were shown to be of value in revealing the tissue or tissues primarily responsible for unusual weight. In comparing breadth of subcutaneous tissue in the calf of the leg with weight or length, one would not expect the positions for these measurements to be closely alike. Body length would not affect the subcutaneous tissue measurement directly, as it would body weight. Furthermore, general retardation in physical development at the infantile level would lead to short stature, narrow pelvis, and hence relatively light weight, whereas it would tend to keep the breadth of subcutaneous tissue relatively large. However, one would expect to have the latter measurement influence body weight and hence to fluctuate, to a degree, with it. It is for this reason that the measurement of subcutaneous tissue has value in interpreting body weight.

CONCLUSIONS

The thickness of subcutaneous tissue has been shown to increase rapidly up to 9 months of age, then to decrease abruptly and rapidly until $2\frac{1}{2}$ years of age and more slowly until about $5\frac{1}{2}$ years of age. The actual thickness at $5\frac{1}{2}$ years is, on the average, about one-half that at 9 months. Between $5\frac{1}{2}$ and 11 years of age the amount remains unchanged, but between 11 and 13 years of age there is a definite increase which appears to be the beginning of an adolescent accumulation. Two few children have been followed more than thirteen years in this study to plot the average trend beyond that age.

These studies show clearly that girls tend to have more subcutaneous tissue than boys throughout childhood, the 10th percentile for girls being close to the 50th percentile for boys at all ages after 2 years, and at certain ages, surpassing it. These norms do not show any earlier increase in connection with adolescence

among girls than boys as might be expected, but this may be due to the small number of cases included at these older ages.

There is great variability in this measurement between individuals of the same age and sex, especially among infants, and as adolescence approaches. Most children tend to remain in approximately the same part of the range during most of the growth period and to return to it after temporary digressions. They are more inconsistent in this respect in infancy than in childhood. Cases showing various unusual trends have been studied.

Judgments respecting the physical development and nutritional status of children could frequently be improved if the normal variations and trends of amount of subcutaneous tissue were more fully taken into account in interpreting clinical findings and body measurements.

The clinician can recognize differences in the amount of this tissue in different children, but he has difficulty in knowing what significance to attach to them. These must be interpreted in the light of normal occurrences for age, sex, and build, as well as on the basis of history and other clinical findings.

The subjective evaluation of the amount of subcutaneous tissue as customarily determined can serve the experienced physician well in determining status at a single examination. The rating thus given is not usually precise enough to recognize changes between examinations or long-range trends during the growth period.

The principal purpose served by studies of shadows of this tissue in roentgenograms is to contribute to our knowledge of growth in this respect and thereby to improve clinical interpretations. However, the method discussed in this paper can be applied readily by any x-ray technician and might well be used clinically in the study of children exhibiting unusual growth patterns.

It is appreciated that the amount of subcutaneous tissue in the calf may not always reflect the situation in other parts and may be less subject to variation with transitory health and dietary conditions than the looser connective tissues over the upper arm or abdomen. It does appear to be a relatively stable area in which to study persistent individual characteristics or long-range changes.

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for short periods, remaining at other times in much the same position within the range. Some deviations in the curves are quite clearly exaggerations of normal trends, as, for examples, temporary obesity between 6 and 9 months of age, or excessive loss of soft tissue between 3 and 5 years of age. However, others appear to be related to nutritional factors, disease, or possibly to habits or environment.

Examples of unusual growth patterns, representing some of the types referred to, are presented in Figs. 3, 4, and 5. In the legends to these figures, brief summaries of pertinent clinical data are given to show the most striking relationships, but no attempt has been made to study or present exhaustively all possibly related information available in the records. The purpose here is not to establish the causes for individual variations but merely to call attention to the types which have been recognized. It is proposed, in subsequent reports, to correlate amount of subcutaneous tissue with dietary and other factors and to present more nearly complete case histories.

In the accompanying figures the percentiles for body length and weight by age for a few cases are given in order to show to what extent position in the ranges for these measurements has varied at the times of the unusual trends in the amount of subcutaneous tissue. In a previous publication⁵ one of us presented graphs for a number of children which allowed comparisons between the status held and progress made in weight, length, breadth of pelvis, and amounts of bone, muscle, and subcutaneous tissue in the calf. The latter measurements were shown to be of value in revealing the tissue or tissues primarily responsible for unusual weight. In comparing breadth of subcutaneous tissue in the calf of the leg with weight or length, one would not expect the positions for these measurements to be closely alike. Body length would not affect the subcutaneous tissue measurement directly, as it would body weight. Furthermore, general retardation in physical development at the infantile level would lead to short stature, narrow pelvis, and hence relatively light weight, whereas it would tend to keep the breadth of subcutaneous tissue relatively large. However, one would expect to have the latter measurement influence body weight and hence to fluctuate, to a degree, with it. It is for this reason that the measurement of subcutaneous tissue has value in interpreting body weight.

CONCLUSIONS

The thickness of subcutaneous tissue has been shown to increase rapidly up to 9 months of age, then to decrease abruptly and rapidly until $2\frac{1}{2}$ years of age and more slowly until about $5\frac{1}{2}$ years of age. The actual thickness at $5\frac{1}{2}$ years is, on the average, about one-half that at 9 months. Between $5\frac{1}{2}$ and 11 years of age the amount remains unchanged, but between 11 and 13 years of age there is a definite increase which appears to be the beginning of an adolescent accumulation. Two few children have been followed more than thirteen years in this study to plot the average trend beyond that age.

These studies show clearly that girls tend to have more subcutaneous tissue than boys throughout childhood, the 10th percentile for girls being close to the 50th percentile for boys at all ages after 2 years, and at certain ages, surpassing it. These norms do not show any earlier increase in connection with adolescence

among girls than boys as might be expected, but this may be due to the small number of cases included at these older ages.

There is great variability in this measurement between individuals of the same age and sex, especially among infants, and as adolescence approaches. Most children tend to remain in approximately the same part of the range during most of the growth period and to return to it after temporary digressions. They are more inconsistent in this respect in infancy than in childhood. Cases showing various unusual trends have been studied.

Judgments respecting the physical development and nutritional status of children could frequently be improved if the normal variations and trends of amount of subcutaneous tissue were more fully taken into account in interpreting clinical findings and body measurements.

The clinician can recognize differences in the amount of this tissue in different children, but he has difficulty in knowing what significance to attach to them. These must be interpreted in the light of normal occurrences for age, sex, and build, as well as on the basis of history and other clinical findings.

The subjective evaluation of the amount of subcutaneous tissue as customarily determined can serve the experienced physician well in determining status at a single examination. The rating thus given is not usually precise enough to recognize changes between examinations or long-range trends during the growth period.

The principal purpose served by studies of shadows of this tissue in roentgenograms is to contribute to our knowledge of growth in this respect and thereby to improve clinical interpretations. However, the method discussed in this paper can be applied readily by any x-ray technician and might well be used clinically in the study of children exhibiting unusual growth patterns.

It is appreciated that the amount of subcutaneous tissue in the calf may not always reflect the situation in other parts and may be less subject to variation with transitory health and dietary conditions than the looser connective tissues over the upper arm or abdomen. It does appear to be a relatively stable area in which to study persistent individual characteristics or long-range changes.

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A FIFTEEN-YEAR STUDY OF PREMATURETY

FROM THE STANDPOINT OF INCIDENCE, MORTALITY, AND SURVIVAL

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THIS is a clinical and statistical survey of premature infants born in the Philadelphia Lying-In, a branch of the Pennsylvania Hospital, encompassing a period of fifteen years beginning Jan. 1, 1930, and ending Dec. 31, 1944. It was in the fall of 1929 that the new maternity building, equipped with nurseries capable of accommodating 125 newborn infants simultaneously, first opened its doors. During the time covered by this investigation, there were 33,668 babies born of which 2,960 were premature, a yearly average of 197. In determining the prematurity of an infant, the regulation issued by the Bureau of Vital Statistics in 1930 was carefully observed. In that year, this regulation stipulated that for any baby of twenty weeks' or more gestation a birth certificate must be furnished and, in case of death, a death certificate. Early in 1943, the ruling was altered, reducing the gestation period to sixteen weeks. This action could be expected to, and did, bring into our statistics an increased number of very small babies that previously had been classified as abortions. The upper limit of prematurity was set at $5\frac{1}{2}$ pounds (2,500 Gm.) which is in conformity with the concepts of the American Academy of Pediatrics. Quite naturally, this upper limit was bound to include full-term babies who were regarded as immature or, as frequently occurred, were of a multiple birth. In collecting the data presented here, these criteria have been faithfully followed. It is obvious that all the details concerning such a large group of premature infants cannot be discussed in one contribution. Some of the more significant and pertinent findings will be given and it is hoped that more will reach publication in the near future.

In assessing the causes of prematurity, there are still a large number of intangible factors which are hard to evaluate properly as to their relative importance. The usual causes have been encountered in this series, such as the presence of a multiple birth, syphilis, toxemia, placental abnormalities, defective maternal genital tracts, acute and/or chronic illness of the mother with termination of pregnancy necessary to preserve her life, emergency surgical procedures that had to be instituted regardless of the baby, and the adherence to the legal requirements of the Bureau of Vital Statistics in determining the gestation period. There were over 400 cases of premature rupture of the membranes, about one-fifth being accounted for by accidents to the mother, but no adequate explanation could be found for the other four-fifths. Most of our preivable babies made up a group for which no reason could be discovered

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to explain why they were not carried to term. In the early years of this study, it was difficult to secure the interest of the obstetric staff in any attempt to determine the etiology in these cases, but as time progressed and we were able to prove that our greatest mortality occurred under such circumstances, our records improved.

The pursuant data on the incidence of prematurity, factors influencing mortality, and pertinent observations on the survival of premature infants will be discussed.

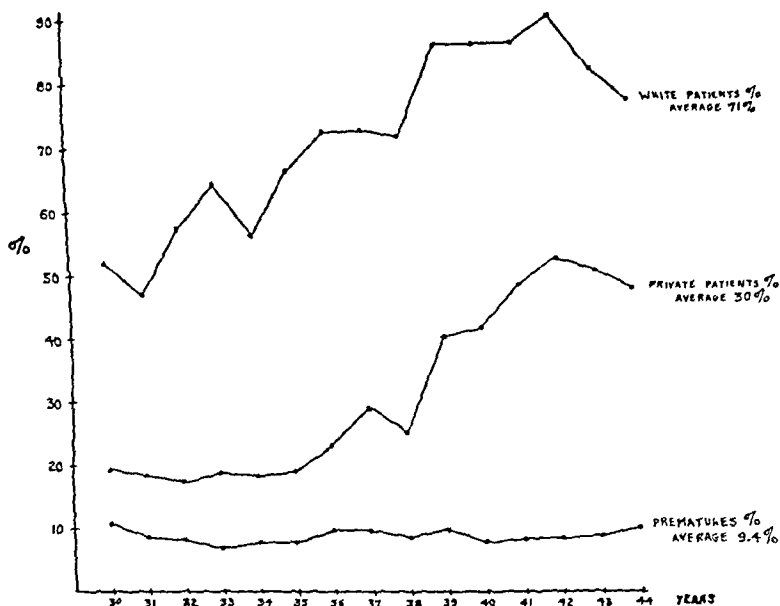


Chart 1.—The incidence of prematurity.

INCIDENCE OF PREMATUREITY

In studying the occurrence of premature babies in the fifteen years of this report, only a slight annual fluctuation was noted during the entire period of time. It appears that all our efforts to bring about a reduction in premature births have been fruitless, but a number of significant facts have been uncovered that are worthy of recording, particularly the one of dietary control initiated in 1932. Chart 1 establishes the fact that the average per cent of premature infants was 9.4, with the highest incidence of 10.2 occurring in 1930, and the lowest of 7.5 in 1933. On the same chart may be noted the decided increase in the percentage of private patients from 19.6 in 1930, to 47.4 in 1944. As the personnel of the obstetric staff increased, there was a concomitant acquisition of more private patients through this circumstance and the hospital devoted more of its facilities, from then on, to caring for a responsible group of women, with less space being available for charity cases. As a result, during the fifteen years, 30 per cent of all premature babies were private patients and these babies, with few exceptions, were given prenatal care and delivered by

recognized obstetricians. The ward patients were attended by residents and interns. Chart 1 shows also a marked increase in the number of white patients, from 52 per cent in 1930, to 71 per cent in 1944, and during the years 1939, 1940, 1941, and 1942, they constituted well over 80 per cent of all cases. The average of white patients among our premature infants for the entire period was 71 per cent. Despite this situation, which developed gradually through the years, there was no obvious favorable response in the number of premature deliveries.

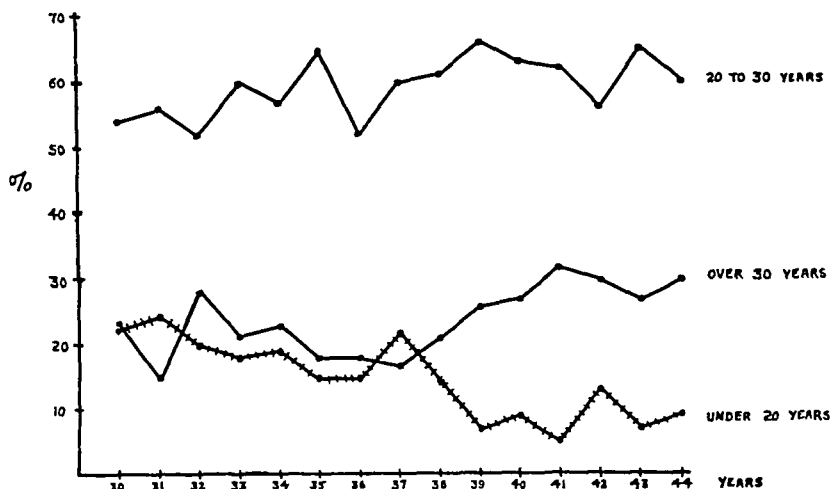


Chart 2.—The age of the mother.

Age of the Mother.—The influence this factor plays in the production of prematurity has been commented upon in medical literature, but too few cases have been included and the surveys have not been continued over a long enough period of time to be conclusive. In order to reflect the comparative ages of the mothers of our premature babies, they were divided into three groups (Chart 2) and it was discovered that the greatest incidence appeared in mothers between 20 and 30 years of age, constituting 59 per cent of the cases over the entire period covered by this survey. There was found also a tendency for the number of premature infants to increase in this age group during the fifteen years, while mothers under 20 years of age, comprising about 20 per cent at the beginning of this study, less frequently failed to reach full term from 1937 on, averaging only 10 per cent. At the same time more mothers over 30 years of age were delivered after 1937, an increase from about 20 to over 30 per cent. It is noteworthy that more mothers over 30 years of age participated in both full-term and premature births. The decline in the number of mothers under 20 years can be ascribed to the fewer Negro patients who, in the early years, constituted a considerable group of very young, unmarried, and immature girls. This shifting of age groups from the poorer class of women to the more stable and economically solvent ones does not seem to have influenced the course of events.

Prenatal Care.—So many changes have taken place in the details of prenatal care in our institution during the time covered by this survey that the only common denominator remaining for the purpose of this paper is the number of prenatal visits made by each patient. The minimum deemed necessary for satisfactory care has been arbitrarily set at four per patient, but at the same time it is recognized that without understanding and skillful medical attention and the cooperation of the mother, the number of prenatal visits assumes less importance. In 1930, only 40 per cent of the pregnant women fulfilled these minimum requirements, but, in 1944, well over 90 per cent had cooperated, most of them receiving as much care as was considered adequate. Not only was improvement noted in attendance for routine examinations, but a diligent effort was made to stress diet and vitamins as an important part of prenatal care.

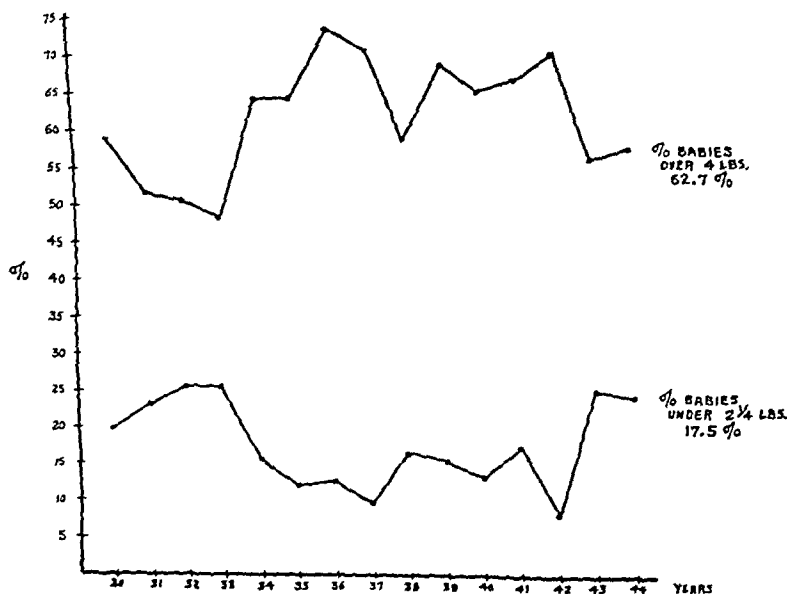


Chart 3.—The incidence of big and small premature babies.

To what extent it succeeded is shown in Chart 3. In November, 1932, a motion was passed by the Staff recommending that a diet containing greater amounts of vitamins, proteins, and minerals be insisted upon for all patients during their prenatal course. While it was not a well-controlled effort and had no obvious effect on the number of premature infants, it apparently had a definite influence on the occurrence of increasing numbers of big premature infants (over 4 pounds) and of decreasing numbers of previable babies under 2 1/4 pounds (1,000 Gm.). This was consistently true with the exception of the period of time when the term of gestation was reduced from twenty weeks to sixteen weeks in May, 1943. However, one of our staff obstetricians was able to effectively demonstrate the value of a scientifically controlled diet during pregnancy. A group of 750 expectant mothers was given a special diet containing large amounts of proteins, vitamins, and minerals with definite limitation

of fluids and water-embracing fruits.¹ Adequate supervision was secured by having one physician examine all patients, one nurse make all home visits, and the hospital issue all dietary instructions. Not one case of prematurity occurred in this group, while there were 37 cases in a similar group not on the special diet.

MORTALITY

Of the many factors influencing the mortality of premature infants, there are several outstanding ones which are of immediate importance. It must be understood that this report applies only to the time during which the patient remained in the maternity hospital and that a good many of the large premature infants were allowed to go home after two weeks, provided their weight was above 5 pounds and they were established on a satisfactory feeding schedule. However, most of these infants remained for an extended period of time, often for as long as three months. The mortality of this series of 2,960 cases has been analyzed from the following standpoints: relationship to total infant mortality, stillbirths and neonatal deaths, length of life, birth weight, sex, age of mother, multiple births, emergencies, syphilis, toxemia, cord and/or placental complications, and methods of delivery.

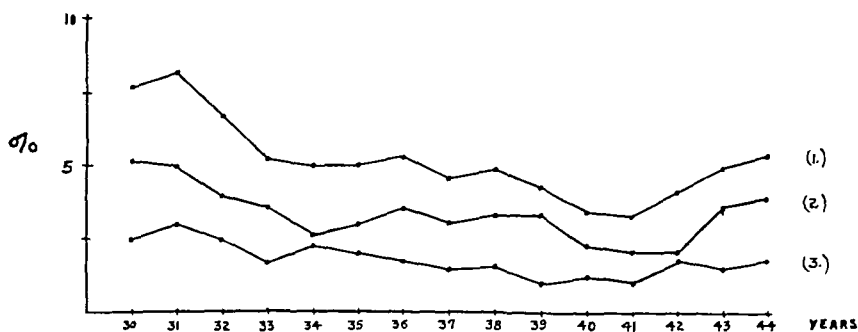


Chart 4.—Mortality. 1, total deaths 5.1 per cent. 2, premature deaths 3.3 per cent. 3, full-term deaths 1.8 per cent.

For purposes of comparison, data on full-term and premature mortality, based on 33,668 babies delivered during the fifteen-year period, are given in Chart 4. There were 600 full-term babies among the 1,740 infant deaths, averaging 1.8 per cent of the total, with the highest mortality (3.2 per cent) occurring in 1931, and the lowest (1 per cent) in 1941. The remaining 1,140 deaths were of premature infants, averaging 3.3 per cent of the total with the greatest number of deaths (5.2 per cent) taking place in 1930, and the lowest (2 per cent) in 1942. The total mortality of the entire group, comprising 30,708 full-term babies and 2,960 premature ones, was 5.1 per cent.

Of the 2,960 premature infants born during this time, 1,140 (38.5 per cent) died. The yearly fluctuation is shown in Chart 5. The highest premature infant mortality (56 per cent) occurred in 1931, and the lowest (26 per cent) in 1940 and 1941. For the seven years from 1934 to 1941, our premature infant mortality was under 35 per cent. There is no question of doubt that the birth

weight of premature infants is an important factor in their survival. As the number of big babies (over 4 pounds) increased in 1934, and the number of previable babies (under 2¼ pounds) decreased that same year, the total mortality among our premature infants dropped decidedly. The greatest influx of previable infants occurred in 1944, there being 50 such cases with 27 under 1 pound in weight. As a matter of interest, there were 182 babies, 1 pound in

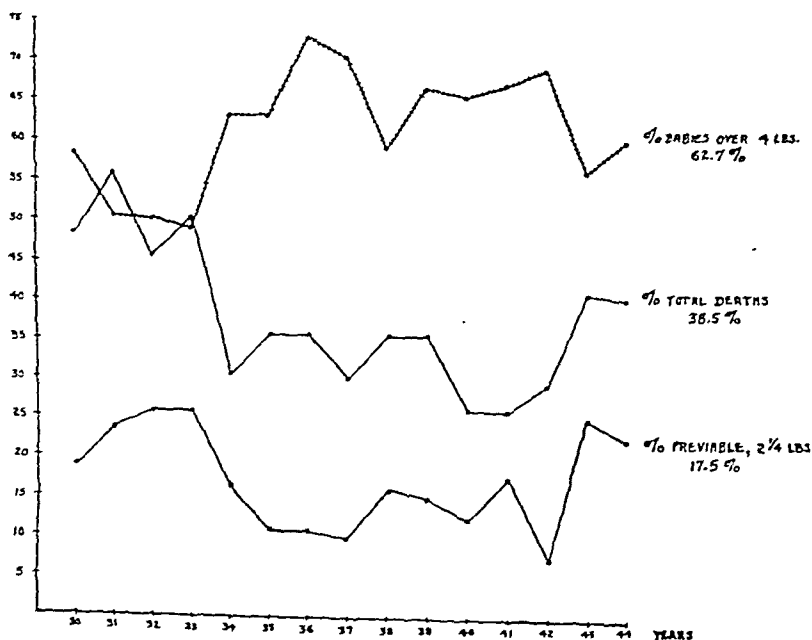


Chart 5.—Relation of deaths to percentages of previable and of big babies.

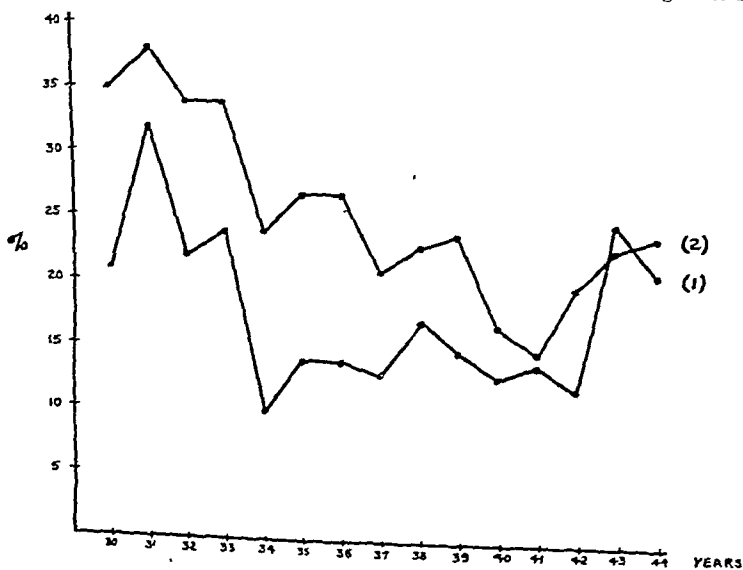


Chart 6.—Yearly fluctuations. 1, stillbirths. 2, neonatal deaths.

weight or under, born during the fifteen years and they are included in this report. The mortality rate also increased suddenly in 1943, when there was a decided preponderance of small babies with a corresponding diminution in the number of large ones. However, the lower mortality rate of between 30 and 35 per cent remained at that level due to the fact that the incidence of large and small babies was reasonably constant from 1934 to 1942. Again it seems apparent that the latest ruling of the Bureau of Vital Statistics (sixteen weeks' gestation period) has been at least partially responsible for these facts. On the other hand, we must consider the part World War II has played, introducing emotional strain into the daily lives of ordinarily calm women, as well as financial instability, and the appalling though understandable tendency to travel all over the country under adverse conditions in order to be with their husbands.

In classifying the 1,140 premature infant deaths, there were found to be 522 stillbirths and 618 neonatal deaths (Chart 6). Any baby who had no heart beat at birth, who made no voluntary respiratory effort, and who demonstrated no muscular movements was classified as a stillbirth. The presence of any one of these reactions immediately placed the child in the category of a neonatal death. Stillborn infants made up 17.6 per cent of the total premature births, the greatest number (32 per cent) occurring in 1931, and the lowest (15 per cent) in 1934. Of the 618 neonatal deaths, 501 infants died in the first forty-eight hours, 164 dying in the delivery room (living from five to sixty minutes), making the mortality in the first forty-eight hours 20.8 per cent, based on 2,438 premature infants born alive. Also 81 per cent (501) of our 618 neonatal deaths were in the first forty-eight hours and 19 per cent afterward. If the 164 babies who died in the delivery room are excluded from the total number of living premature babies, then only 2,274 premature infants were admitted to the nurseries. On that basis, the mortality of the first forty-eight hours is 14.8 per cent and the mortality after this time is 4.8 per cent. Of the 501 premature infants unable to survive the first forty-eight hours, 458 (74 per cent) died during the first twenty-four hours of life, and 43 (7 per cent) in the second twenty-four hours.

Babies who are born dead and those who die within the first two days of life die, in most instances, as the result of complications of pregnancy, labor, and delivery. The responsibility for such deaths cannot always be attributed to one definite factor but is usually a combination of more than one. It appears from our experience that heroic efforts exerted under these conditions will save only a few babies. One wonders whether the reason for this can be attributed to failure of our technique or whether it is the result of what has existed before and during birth. The babies who die after the second day allow the pediatrician sufficient time for clinical observation and laboratory study, enabling him to more certainly assign the death to a specific pathologic condition. There were 117 premature deaths occurring after the first forty-eight hours, and autopsies in 60 cases revealed the immediate causes of death to be as follows: pneumonia, 31; malformations, 10; diarrhea, 3; hemorrhagic disease, 2; erythroblastosis fetalis, 1; meningitis, 2; septicemia, 2; prematurity, 29; unknown, 12; and intracranial hemorrhage, 6 (delivery complication). Systemic and pathologic con-

ditions of the mother which made survival extremely unlikely included placental and/or cord anomalies, 4; toxemia, 4; syphilis, 7; and other diseases or illness, 4.

Sex.—Contrary to what has frequently been reported, our records reveal that there were more female than male premature infants and that the mortality was higher in the males by more than 8 per cent. There were 1,418 male premature babies of whom 608 (42.8 per cent) died and 1,542 female infants of whom 532 (34.5 per cent) succumbed. The relative numbers of premature infants of both sexes were fairly uniform throughout the period, as were the deaths.

TABLE I. AGE OF MOTHER IN RELATION TO MORTALITY OF PREMATURE INFANTS

	TOTAL CASES (%)	TOTAL MORTALITY (%)	GROUP MORTALITY (%)
20 to 30 yr.	59	53	34
Under 20 yr.	16	15	35
Over 30 yr.	25	31	50

Age of the Mother.—It has been shown previously (Chart 1) and also in Table I that 59 per cent of our premature infants were born to mothers between the ages of 20 and 30 years, accounting for 53 per cent of our total infant deaths, while the mortality rate in this group alone was only 34 per cent. Mothers under 20 years of age, comprising 16 per cent of the premature deliveries, accounted for 15 per cent of the total infant deaths with a mortality of 35 per cent. Mothers over 30 years of age gave birth to 25 per cent of the premature babies, accounting for 31 per cent of all the premature deaths, but the mortality in this group was 50 per cent. It would appear from these statistics that premature babies born to mothers over 30 years of age are less viable and do not have the ability to survive which is more apparent in those babies born prematurely to mothers of younger age. The reason underlying this observation is obscure.

Multiple Births.—Infants, premature as a result of a multiple birth, have a lower mortality percentage than do single premature infants.² Twins are more likely to be a little larger, less immature, and closer to full term than single premature infants. In our group, there were 169 sets of twins, both babies included, and there also were 57 siblings of twins, the other twin being above our upper weight limit and, therefore, not included. There were two sets of triplets (all of one set died) and one set of quadruplets. Among our premature births, there were 405 babies of multiple births of whom 127 (31 per cent) died. In Table II is shown the mortality of first- and second-born twins

TABLE II. MORTALITY OF FIRST AND SECOND TWIN

First twin	
Under 3 pounds	89%
Over 3 pounds	11%
Total	29.5%
Second twin	
Under 3 pounds	95%
Over 3 pounds	16%
Total	33%

according to whether they were under or over 3 pounds birth weight. Twenty-two per cent of the twins were under and 78 per cent over 3 pounds. It appears more dangerous to be the second of twins.

Emergency Cases.—During the fifteen years of this survey, there were 381 (12.8 per cent) unregistered emergency cases and of this number, 245 (64 per cent) died. In 1930, almost 40 per cent of our total premature births belonged in this category, while in 1944, only 6.8 per cent did. As the hospital developed and began to accept more private patients, accommodating fewer Negro patients, the number of emergency deliveries decreased. Another contributing factor was the definitely improved attitude of all patients, particularly in their cooperation with regard to prenatal care, but in spite of these changes the mortality rate of this group of cases remained constantly high throughout the entire time.

Syphilis.—Positive Wassermann reactions were found in 207 (7 per cent) of the mothers. From 1930 to 1935, there were 116 such cases and only 91 in the following ten years. This improvement was due in large measure to the elimination of uncooperative Negro mothers but directly was the result of intensive syphilitic chemotherapy in recent years.

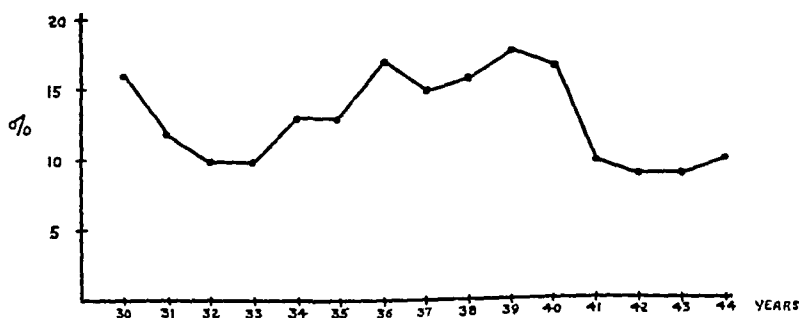


Chart 7.—Incidence percentage of toxemia among mothers of premature babies.

Toxemia.—The relationship of toxemia of pregnancy to the mortality of premature infants has provoked considerable discussion. In this study, there have been 386 such cases with 143 (37 per cent) deaths, although its occurrence has fluctuated somewhat during the fifteen-year period. The highest incidence occurred in 1939 with 18 per cent, and the lowest in 1942 and 1943 with 9 per cent (Chart 7). The fluctuation is shown on the graph. These were well-defined cases and did not include the many others of ankle edema.

TABLE III. TOXEMIA

	CASES (%)	DEATHS (%)	COMPLICATIONS (%)
Group I (over 4 pounds)	61	21.5	77.7
Group II (3-4 pounds)	19	45.7	60.0
Group III (under 3 pounds)	20	75.0	39.0

In order to illustrate the relationship between toxemia of pregnancy, complications, and birth weight of premature babies, the 386 cases have been di-

vided into three groups (Table III) of which 143 died, and 82 of these deaths were accompanied by complications. The complications encountered included syphilis, cord and/or placental conditions, accidents of delivery, and processes in the child inimical to life. Group I, made up of babies weighing over 4 pounds, has the most cases but, at the same time, it has the lowest percentage of deaths and the highest percentage of complications in those deaths, the complications being the most important item in the mortality. In Group II, the size of the baby and the complications encountered in the fatal cases were of about equal importance as causes of inability to survive, while Group III had the lowest number of complications in the fatal cases and the highest percentage of deaths. It can be stated that Group III is a most dramatic reminder of how important the size of the baby is in its fight for life and it would appear to be more important than toxemia itself.

Cord and Placental Complications.—The complications of pregnancy, labor, and delivery may represent danger to the mother, but they are always far more dangerous to the infant. Conditions affecting the cord, such as prolapse, knots, twist's, malformations, or loops about a part of the body, must be dealt with promptly, generally by some form of operative obstetric procedure. Placental abnormalities such as placenta previa, premature separation, fibrosis, calcification, infarction, and necrosis are all dangerous to the life of the child. In Table IV is shown the number of such cases together with the number of stillbirths and neonatal deaths. When these particular types of complications are considered from the standpoint of the birth weight of the child, it is found that of the 436 babies, 146, or 33 per cent, weighed under 3 pounds and the mortality rate was 94 per cent. There were 141 deaths in this weight group and 123 of them were definitely related to the coexisting complication. Of the entire 436 babies, 290 (66 per cent) weighed over 3 pounds and 134 (46 per cent) died. In 115 of these deaths, there was a definite relationship between the death and the specific complication.

TABLE IV. INFLUENCE OF CORD AND PLACENTAL CONDITIONS

	TOTAL CASES	LIVING	STILL- BIRTHS	NEONATAL DEATHS	TOTAL DEATHS	% OF DEATHS
Cord	110	67	49	24	73	52
Placenta previa	73	28	11	34	45	61
Placental separation	140	45	50	45	95	68
Placental defects	83	19	48	16	64	77
Total	436	157	158	119	277	63

In considering the role of these pathologic contingencies of pregnancy with regard to the prematurity mortality, the ratio between babies over 3 pounds and under 3 pounds is 2 to 1. From the same standpoint, the ratio in cord complications is 3 to 1; in placenta previa, 2 to 1; and in placental separation and placental defects combined, 3 to 2. Since the proportion of small babies (under 3 pounds) is greater in placental than in cord complications, the mortality can also be expected to be higher. When the 140 cases of placental separation and the 83 cases of placental defects are combined, we find that they comprise 51 per cent of the total babies in this group and 58 per cent of the fatal

ities. It is interesting to note that neonatal deaths are greater in placenta previa cases while stillbirths are higher in cord abnormalities, placental separation, and placental defect cases. In view of these facts, it is evident that birth weight is a matter for deep consideration when coupled with cord and placental complications, apparently being the reason for the high mortality in placental separation and defects. However, there is no question about the seriousness of cord and placental complications of pregnancy and, while birth weight is influential, the extent of the complication, and the time element involved between the onset of the condition, the moment it is diagnosed, and the appropriate action taken, are far more important. The mortality of this portion of our prematurity cases is 63 per cent. In relation to the 2,534 babies who did not experience these difficulties, the mortality is only 34 per cent but the ratio of babies over, to those under, 3 pounds is 4 to 1.

The cause of death in many of these babies can be ascribed to asphyxia. The clinical course followed by them consisted of repeated cyanotic attacks, listlessness, inactivity, poor feeding ability, temperature fluctuations, and convulsive symptoms. The autopsy findings showed generalized congestion, petechial and massive hemorrhages in various organs, and considerable edema of the brain.

TABLE V. METHOD OF DELIVERY IN RELATION TO PREMATURE MORTALITY

METHOD OF DELIVERY	CASES	TOTAL DELIVERIES (%)	UNDER 3 POUNDS	COMPLICA- TIONS	DEATHS (%)
Spontaneous vertex	1238	41	37	42	50
Forceps on vertex	921	31	3	28	11
Breech	411	13	42	42	60
Version	121	4	15	30	35
Cesarean section	269	9	19	94	40

Method of Delivery.—The implication in numerous articles regarding the relationship between the method used to deliver premature babies and their mortality³ appears to be erroneous after considering Table V. Here there has been no selection of cases for any reason whatsoever, either favorable or unfavorable to any particular method of delivery. The figures given constitute an over-all picture of the relationship between mortality (both stillbirths and neonatal deaths) and delivery methods in this series of 2,960 premature births. It would seem that there are factors more important than the type of delivery employed. It would be most unwise to consider alone the fact that 50 per cent of the infants born by spontaneous vertex presentation (comprising 41 per cent of the total premature deliveries) had died, without also considering the fact that 37 per cent of these babies weighed less than 3 pounds at birth. At the same time, it was in this group that the greatest number of emergencies without prenatal care existed—babies born on the way to the hospital or immediately after admission. An appreciable number of them were known to be dead babies and the method of delivery selected was the best one for the safety of the mother. Of primary importance were the complicating factors in both mother and child which brought about the premature birth, such as syphilis, toxemia, placental and cord conditions, accidents, and other systemic diseases of the mother in-

compatible with a full-term pregnancy, as well as intracranial hemorrhage, pneumonia, malformations, and Rh incompatibility on the part of the baby. There were also a number of habitual aborters and women who had in the past given birth to premature infants.

Forceps applied to the vertex constituted 31 per cent of the total with a mortality of only 11 per cent. Superficially, these percentages could be interpreted as signifying that this is a safer way to deliver a premature infant, but when other information is examined, a different viewpoint is obtained, for only 3 per cent of these babies weighed under 3 pounds and there were maternal or fetal complications in but 28 per cent of the cases. The difficulties encountered in this group were definitely less severe and of less importance than those occurring in the spontaneous vertex deliveries. It is of interest to note that there has been a consistent increase in the number of forceps deliveries, corresponding somewhat with the more frequent occurrence of large premature babies weighing over 4 pounds.

The highest mortality among our premature infants took place in breech deliveries. Of the 13 per cent breech deliveries, 60 per cent did not survive. There was very little variation in the number of premature infants delivered by this method throughout the fifteen-year period, and it is significant that 42 per cent of them weighed under 3 pounds, which is a decidedly high incidence of small babies. The maternal and fetal complicating factors in this group averaged 42 per cent and also were of the more dangerous type. It can be stated with safety that breech delivery is the most hazardous of ordeals for the premature infant.

Versions comprised 4 per cent of the total premature deliveries with a mortality of 35 per cent, being employed in three-fifths of the cases in delivering the second of twins. A number of these were elective versions for reasons other than multiple birth. Only 15 per cent of the babies were under 3 pounds birth weight and 30 per cent were accompanied by anomalies, the most serious one being the malposition of the baby. Other than the existence of a multiple birth, the difficulties attending this type of delivery were not too severe in character and the method has been used with decreasing frequency. It has the second lowest mortality and second lowest number of complications. It might be well to give this method of delivery more attention.

The advisability of performing a cesarean section to deliver premature babies has always been a hotly disputed problem. Nine per cent of our patients were delivered in this manner with a resulting mortality of 40 per cent which, on the surface, appears highly significant. However, when we realize that 19 per cent of the babies weighed under 3 pounds and that 94 per cent were attended by maternal complications demanding immediate intervention, the picture assumes an entirely different perspective. Most of these were emergencies where some action was needed promptly, not only for the survival of the child but, in many instances, to preserve the life of the mother. As is always the case in situations of this kind, the additional danger of shock to the baby was encountered, caused not only by hemorrhage and the rather deep anesthesia necessary for such an operative procedure, but particularly attributable to the time

element involved from the onset of the acute symptoms to the point at which the baby was born, the extent of anoxemia, and the depth of respirations. There is no question of doubt that more cesarean sections are being performed. In the first five years of this survey, only 6 per cent of the premature infants were delivered in this manner, but in the last ten years the incidence has risen to 10 per cent.

For means of comparison, in view of these remarks on the relative merits of different methods of delivery, a rather rough survey of fetal mortality was made in over 24,000 births of full-term infants whose birth weights were over 2,500 Gm. (5½ pounds) with the following results: vertex 2.1 per cent, forceps 1.4 per cent, breech 7.6 per cent, version 3.8 per cent, and cesarean section 4.1 per cent. A complete survey will be given when the deaths of full-term infants are analyzed.

SURVIVAL OF PREMATURE INFANTS

The chances for survival of a premature infant depend more on what occurs before and during delivery than it does on what happens afterward. Of the many factors influencing their ability to live, the outstanding one is birth weight. The nearer to full-term the child is carried and the greater the birth weight, the better is the prognosis. Of the 2,960 premature babies under consideration, 1,820 were discharged from the hospital. A few were discharged against advice and are known to have succumbed shortly after, either at home or in another hospital. In Table VI, they are classified according to their weight in pounds.

TABLE VI

WEIGHT	TOTAL	PER CENT OF TOTAL PREMATURES	PER CENT OF SURVIVAL
Under 2 pounds	384	12.9	2
2 to 3 pounds	331	11.1	20
3 to 4 pounds	414	13.9	46
4 to 5 pounds	848	28.6	81
5 to 5½ pounds	982	33.1	91

In the early years of this report, we were constantly asking ourselves why a premature infant did not survive when no obvious answer could be found to explain it in either the prenatal or natal period. The absence of conclusive clinical evidence or of autopsy findings increased our wonderment. Blame was placed on anatomic and physiologic failures¹ in the child, referring particularly to the location of blood vessels in the lungs, whether or not they were too far away from the air vesicles. Others have reported similar findings about the medulla.^{5, 6} Full appreciation of the destructive effects of anoxemia has been slow in coming to our consciousness.

Feeding.—A vital part of our struggle to maintain life in premature babies is concerned with how to feed them. Individual workers in this specialized field have developed effective techniques with various types of milk but it is our belief that a great deal depends on the skill of the pediatrician in manipulating the food in each particular case. Results can be identical, regardless of the food used. Our plan of action has been to withhold all milk feedings during

the first twelve to twenty-four hours, during which time small amounts of boiled water, either with or without sugar, have been offered. It has been our custom to begin with food of low caloric value, gradually increasing it, but seldom exceeding 60 calories per pound body of weight per day, the first consideration being the establishment of good digestion rather than gain in weight. When there is no vomiting or abdominal distention and there are perfectly normal stools, we believe it possible to go ahead with confidence that the gastrointestinal tract is functioning effectively. This is usually accomplished sometime between the seventh and fourteenth days of life and at that time vitamins may be added to the regime. Our choice of food for premature infants has been breast milk, regardless of its supposed deficiency and our faith has been justified, for it has met all the necessary requirements. In one of our numerous attempts to appraise clinically the relative values of foods for premature infants, breast milk, lactic acid certified milk of varying fat percentages, and two dried milk preparations were given to four groups of premature babies whose birth weights were about 4 pounds. While the average daily gain on breast milk was slightly less than on the others, it was the consensus of opinion that the babies were more comfortable on it.⁷

The hours of feeding have varied depending more upon the size and capacity of the child than upon a preconceived nursery regulation. Most of the small babies are fed every two hours, with twelve feedings daily. Changes in the schedule are made in each case to meet the needs of the infant, aiming at a four-hour feeding regime with five to six feedings per day. The two-hour feeding for very small premature infants has been instituted to allow as much fluid as possible by mouth in order to avoid parenteral administration of other fluids, the amounts given at the beginning varying between one-eighth to one-half ounce. As a rule, any increase in the original amount is left to the discretion of the nurse in charge, who is required to confine her activities in this respect within the limitations set by the pediatrician. She is given authority to either reduce or increase the amount at any feeding, the amount depending upon conditions.

The method of feeding is adapted to the individual case, but practically all small infants are fed by gavage because of their poor sucking and swallowing reactions as well as to conserve their energy. In addition, less time is consumed by this procedure. As soon as it is indicated by the condition of the baby, a trial is made with a Breck feeder or a bottle with a small, soft nipple with holes of adequate size, always bearing in mind that the method selected should be the one best suited to the individual child. It is often necessary to proceed cautiously with increases for two weeks before sufficient food can be offered to secure any gain in weight, but by exercising care digestive disturbances are avoided. After good digestion has been established and the food intake is adequate, growth in muscle and bone will follow readily enough.

It has been found wise, particularly when dealing with the very small child, to give oxygen and carbon dioxide (6 per cent) for a few minutes before and after each feeding. This seems to prevent attacks of cyanosis when food is introduced into the stomach, and if cyanosis does occur, that feeding is stopped

Dehydration.—Another troublesome feature of premature infant care is the tendency toward dehydration which is often neither fully appreciated nor recognized early enough by the pediatrician. Careful palpation of the fontanelles and sutures is more certain to give earlier information of the development of this condition than skin turgor and elasticity. When it occurs, our first procedure is to increase fluids by mouth by means of gavage feeding if this is not already employed. Subcutaneous injection of fluids, such as saline or plasma, is not attempted routinely for the reason that a number of bitter experiences have convinced us that too many skin punctures are both serious and dangerous, leading to subcutaneous abscesses. The subcutaneous tissue in premature babies does not tolerate distention well.

Infection.—All infections must be guarded against. When it is realized that incipient infection may be present without local tissue reaction, fever, or changes in white blood cells, we should be doubly alert in our handling of premature babies. The skin of these small infants is particularly vulnerable. Overheating, rough clothes, brusque handling, and meddling surgical procedures have a tendency to irritate the skin and so should be avoided. Impetigo and miliaria, forms of staphylococcic infection, are not only troublesome but also dangerous.⁸

We have been continually amazed during the past fifteen years by the apparent unsusceptibility of previsible babies to upper respiratory infections even during periods of high incidence in the general population and in the presence of milder attacks in the mother.^{9, 10} When pneumonia developed, most of the cases were of the lipoid variety and were usually either the result of insufflation of food, amniotic debris, vaginal secretion, or a terminal phase of sepsis. In the latter condition, the *Staphylococcus aureus* is the most frequent offender followed in importance by colon bacillus, hemolytic streptococcus and *Streptococcus viridans*. The portal of entry is not always found, but the organisms can gain entrance to the blood stream through abrasions of the skin, through the cord stump, through the gastrointestinal, pulmonary and genitourinary tracts, and because of careless intravenous and subcutaneous injections. The development of diarrhea in these babies is extremely hazardous to their survival, and overfeeding in the first few days of life is often a contributing factor. However, *S. hemolyticus*, *Bacillus pyocyaneus*, and *B. coli* have been cultured from both the stools and blood when this condition occurs. Usually a breakdown of the nursery aseptic technique has been at fault, but fortunately this occurrence has been extremely rare. Clean hands and hair on the part of all those handling the babies, exclusion from the nursery of all persons suffering from respiratory or skin infections, no matter how mild, careful supervision of the formulas and their sterility, and individual utensils for each baby comprise the backbone of our nursery technique. For a number of years, caps and masks have been eliminated because of their questionable value in preventing the spread of infection, and the results have appeared to justify this action.

Environment.—The provision for and maintenance of an environment comparable to the protective maternal one from which he has so abruptly been separated is of vital importance to the baby. It is not only necessary to prevent

subnormal temperatures but also to avoid the development of fever in the premature infant, for either can be equally dangerous. The temperature of the incubator or hot bed should be so regulated as to provide the utmost comfort and at the same time to maintain the baby's temperature between 98 and 100° F. which, from our observation, appears to be ideal. The latter should be checked rectally every three hours until such time as stabilization becomes evident. Premature jackets help in conserving the body heat, but are not mandatory, and do prevent motion. Moisture control of the environment should also be watched for it has been our experience to witness a number of small premature infants who showed great signs of discomfort when the relative humidity exceeded 50 per cent. In checking our nurseries, we have found it possible to maintain a relative humidity of between 30 and 45 per cent without any particular effort, and this moisture content has proved both adequate and satisfactory for these small babies. From time to time, they are allowed an opportunity to regulate their own body temperatures by the simple expedient of the heat being turned off temporarily or of the child being removed to an ordinary crib. It is surprising to see how quickly they can adapt themselves to the changed circumstances.

Prognosis.—When considering the ultimate prognosis of those premature babies who survive the early months, time alone will reveal the answer. In the majority of cases, it must be guarded and is dependent more on the inherent vitality of the child plus the normal development and functioning of his anatomic and physiologic processes, than upon the start in life we are able to offer in the hospital. There can be abnormal physical conditions existing at birth which are not demonstrable clinically in the first few weeks but which are detected after several months have elapsed as, for example, focal brain injury indicated by partial spasticity of an arm or leg, serious eye defects, and mental retardation with or without convulsions. The physical growth of premature babies is uncertain in the first few years. We have observed a 2-pound child at birth, who weighed only 12 pounds at one year, and 16 pounds at 2 years of age. On the other hand, several progressed normally as illustrated by a 2-pound, 2-ounce boy who weighed 20 pounds at one year, and 27 at 2 years of age. A checkup on a relatively small group of these premature infants in the Well-Baby Clinic during their first year showed them lagging behind the average full-term babies by 2 to 3 pounds.

However, no matter how dubious the outcome may be, it is still our obligation to provide the best knowledge, medical supervision, and nursing care for premature infants. Success or failure depends, in large measure, upon the efficiency and faithfulness of the nursing staff. Our hospital has been most fortunate in having the services of many nurses in charge of the nurseries who understood the problem facing them and who gave unstintingly of their time and energy in order to carry out our program. Special duty nurses on private cases have been far beyond the average in intelligence and have given competent and full care to their infant patients. It can also be stated that the obstetric and pediatric staffs have been awakened to the exceptional requirements and

If it were felt that the infant was hungry, he was sent to his mother for feeding, was fed water in the nursery, or was given an empty bottle to suck, whenever these efforts did not conflict with the floor routine. Within practical limits the nursery routine was made flexible enough to meet the demands of each situation.

Work charts were made for each twelve hours during the entire time of observation. The crying behavior of each baby was plotted in a horizontal bar divided into twelve parts, each division representing sixty minutes. Each crying period was represented by a straight black line, above which was written the number of minutes of crying and beneath which a letter indicated the probable reason or reasons for each spell; namely, (a) hunger, (b) vomitus, (c) soiled diaper, (d) wet diaper, and (j) unknown reasons, as in the study of last year. Each period of nursing care was similarly plotted using a straight red line, above which was placed the number of minutes of care. "Nursing care" was again used as a rather general term including the time spent changing diapers, taking temperatures, or offering water, as well as the feeding time spent in the mother's or nurse's arms. However, records were kept of the actual amount of time each baby spent in his mother's room, so that the time spent in baby-tending by the nurses could be computed. These work charts gave the data which were analyzed for this report.

RESULTS

The average number of babies occupying the nursery each day was eighteen, which is two less than we had last year. The average number of minutes of crying for each baby in twenty-four hours was 55 minutes, a decrease of 51.4 per cent in the figure of 113.2 minutes determined in the study of 1944. Each baby had an average of eighteen crying spells each day; 5.7 (31.4 per cent) of these spells lasted for more than 3 minutes. This was somewhat higher than the average of four prolonged crying spells observed last year in the study of the newly born babies in the home.³

TABLE I. NUMBER OF CRYING SPELLS PER DAY FOR EACH CAUSE DURING THE STUDIES IN 1944 AND 1945

YEAR	NUMBER OF BABIES PER DAY	CAUSES OF CRYING						
		TOTAL SPELLS PER DAY					PROLONGED SPELLS PER DAY*	
		HUNGER	VOMITUS	SOILED DIAPER	WET DIAPER	UNKNOWN REASONS	HUNGER	UNKNOWN REASONS
1944	50	345 (32.6%)	6 (0.6%)	92 (8.7%)	204 (19.2%)	412 (38.9%)	55.3%	19.8%
	1	6.9	0.1	1.8	4.1	8.2	2.2	0.8
1945	18	137 (37.0%)	5 (1.4%)	25 (6.8%)	88 (23.8%)	115 (31.1%)	61 (44.2%)	26 (22.2%)
	1	7.6	0.3	1.4	4.9	6.3	3.4	1.4

*Study in 1944 on prolonged spells of crying was made in the homes shortly after the babies left the hospital. In 1945, this study was made while the baby was still in the hospital. Crying for more than three minutes was considered prolonged crying.

While the determination of the cause or causes of each crying spell still depended on the personal judgment of each observer, since the observers were more experienced, the information was undoubtedly more nearly accurate than

that obtained in the more casual study of 1944. This may account for the increased number of instances in which there were multiple reasons for crying. Whereas each baby had only eighteen spells of crying per day, twenty reasons for crying were listed daily for the average baby. The number of crying spells in the nursery per day for each cause is shown in Table I. In the investigations of both years, hunger and unknown reasons led the list of causes of crying; but this year the incidence of crying spells due to hunger exceeded those due to unknown causes. Unknown causes were listed in 22.2 per cent of the prolonged episodes of crying. This number should be compared with 19.8 per cent in the study made of the children in their homes in 1944.³ Hunger, on the other hand, accounted for 44.2 per cent of the prolonged spells of crying in the nursery, whereas in the home the mothers estimated this figure at 55.3 per cent. In studying the number of minutes of crying for the total group per day ascribed to each cause (Table II) we found that hunger caused 53.2 per cent of such time and that unknown reasons, the next highest factor, dropped down to 23.3 per cent.

TABLE II. MINUTES OF CRYING PER DAY FOR EACH CAUSE DURING THE STUDIES IN 1944 AND 1945

YEAR	NUMBER OF BABIES PER DAY	CAUSES OF CRYING				
		HUNGER	VOMITUS	SOILED DIAPER	WET DIAPER	UNKNOWN REASONS
1944	50	2,024.2 (35.5%)	26.7 (0.5%)	474.8 (8.3%)	1,169.9 (20.6%)	2,000.6 (35.1%)
	1	40.5	0.5	9.5	23.4	40.0
1945	18	533.7 (53.2%)	5.2 (0.5%)	64.2 (6.4%)	166.2 (16.6%)	233.3 (23.3%)
	1	29.6	0.3	3.6	9.2	13.0

Whereas all of the values for the study in 1945 were less than those for 1944, we found considerable change in the percentage of crying for which each cause was responsible. Thus, while in 1944, hunger accounted for 35.5 per cent of the minutes of crying each day, this figure rose to 53.2 per cent in 1945. While the amount of time due to unknown reasons was 35.1 per cent in 1944, it dropped to 23.3 per cent in 1945. This may be interpreted to mean that the ameliorating regimen stopped much of the crying due to unknown, perhaps less compelling causes, whereas it was unable to quiet babies under the influence of a basic demand like hunger.

During the process of analyzing the data, the sum of all the minutes of crying of all the babies for each hour of the day was determined. From this material the average amount of crying for each baby per hour was calculated. We have summarized these data in Fig. 1 and have included the hourly distribution of crying during the study in 1944. The general reduction in crying demonstrated during this study is shown clearly in Fig. 1. But in two periods of the day in 1945, from eight to ten o'clock in the morning and in the evening, two new peaks of crying appear in the graph. Both of these may be explained by the nursing routines. After the nurses receive the morning report at 7:30 A.M., they come into the nursery to give the babies their morning care. The nurses take the babies' temperatures, clean them, weigh them, and put clean

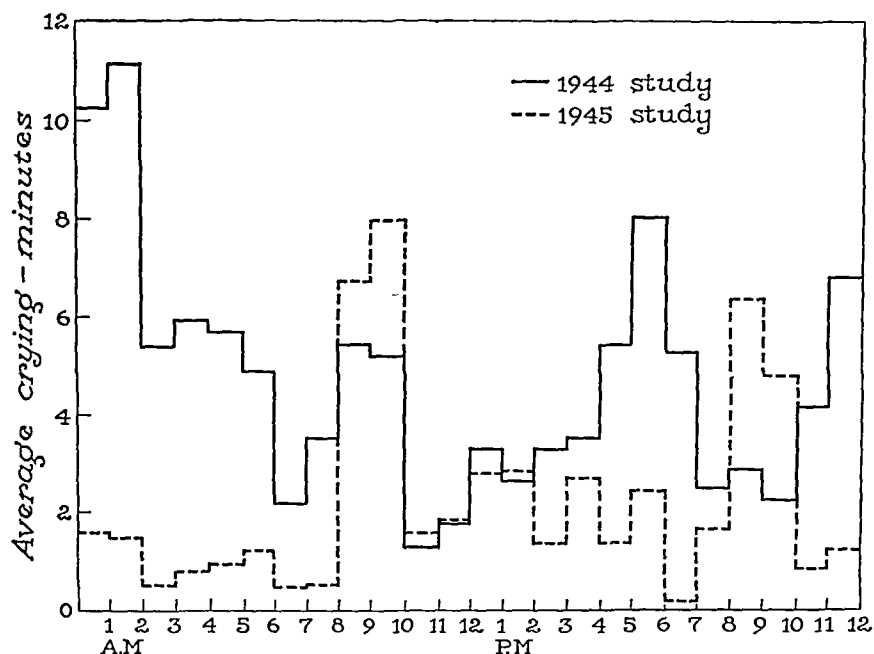


Fig. 1.—Average hourly crying for babies in 1945 compared with that in 1944.

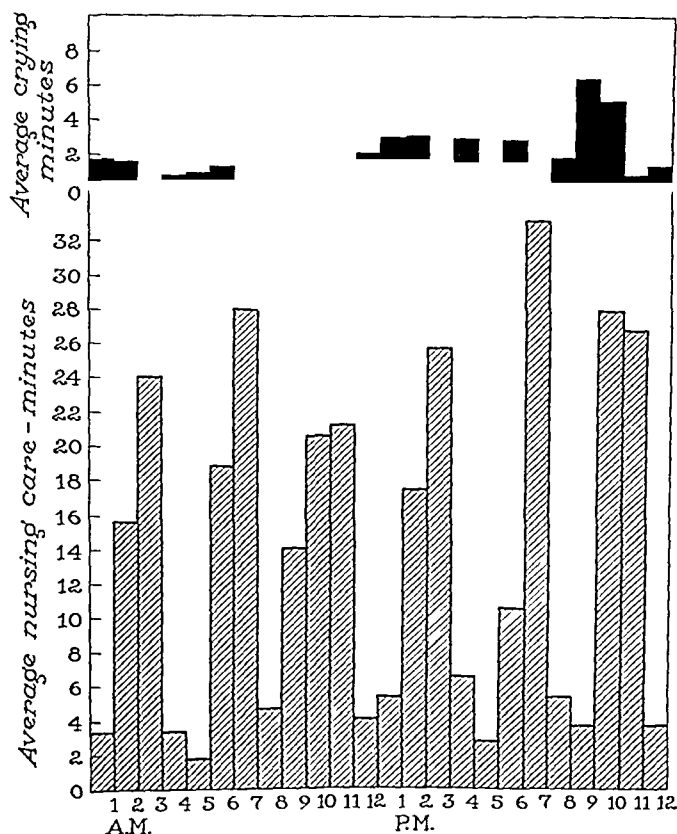


Fig. 2.—Hourly crying compared with the nursing care of babies in 1945.

clothing on them. During this process each baby is thoroughly awakened, after which he is put back into his crib to wait until 10 A.M. for feeding. It is obvious that crying might increase at that time. In the evening any babies who become hungry or uncomfortable must await departure of visitors and routine care of the mothers before they can be taken into their mothers' rooms for comfort or feeding. We feel that these two periods of crying, which exceed the corresponding periods in 1944, can be corrected by appropriate changes in the nursery routines and that with this modification we can still further reduce the amount of crying in the newborn nursery.

The hourly amount of nursing care given each baby was calculated, and these figures were plotted against the amount of crying in the same hours. This is shown in Fig. 2. The spacing of the pillars of nursing care which indicate feeding times is now nearly equal, an improvement over the graph made from the study in 1944 where it was unequal. However, the reciprocal relationship between crying and nursing care is still evident.

By comparing Fig. 2 with the graph made from the study in 1944 the increase in the total amount of nursing care is evident immediately. By actual calculation we found that each baby in the nursery this year received five and one-half hours of care each day. This is seventy-three minutes more than the daily nursing care given each baby in 1944.

However, so far in our calculations nursing care has included the amount of time spent by the babies in their mothers' rooms, so that this five and one-half hours of nursing care were not entirely given by the student and graduate nurses; much of it was provided by mothers. In order to calculate the actual amount of professional care given to babies it was necessary to find out the time spent by each baby in his mother's room. Study of this factor revealed that the mother alone cared for the baby for 3.6 hours daily. Subtracting this 3.6 hours from 5.5 hours, we find that 1.9 hour each day was devoted to each baby by the nurses. Similar calculations reveal that in the 1944 study 0.7 hour each day was devoted to each baby by the nurses. When only 0.7 hour of nursing care was given daily to each baby, the average infant cried 113.2 minutes per day. With an increase to 1.9 hours of care the crying time dropped to 55 minutes.

It may be of interest to know that during the 1945 study 79.3 nurse hours were available each day. These hours are exclusive of those of the supervisor and those of the personnel in the milk laboratory. It is easy to calculate from this that the actual amount of time spent by the nurses with the babies each day was 43.1 per cent of the available time.

The question may be asked how many times does the nurse pick up the baby each day. Our data show fifteen times. In 89.8 per cent of the times that the baby was picked up, the care given took longer than three minutes. Hence, we know that when the nurse picks up a baby for any purpose, it can be expected to take her longer than three minutes.

COMMENT

In our consideration of the neonatal crying problems we have assumed the cry of the newly born baby as an individualized form of self-expression, used

as a signal of need to whomever takes care of him. The cry occurs in response to extrinsic or intrinsic stimuli.

By making changes in the nursing and floor routines, adding more nurses, and individualizing the care, crying in the neonatal period was reduced 51.4 per cent and we estimate that as a result of this study more changes in the nursing routines may come which can further improve the babies' comfort during the stay in the hospital.

It was found in a previous study¹ that barometric pressure might possibly have some effect on the amount of crying, but since the barometric pressure was consistently higher during the study in 1945 than in 1944, and since we had a decrease in the amount of crying in the 1945 study, this factor cannot have been of any great significance.

Hunger and unknown reasons remain the most important causes for crying. It is apparent from the increased percentage of the crying for hunger that this factor must be treated appropriately by feeding the baby when he shows the need for food. Such treatment will require modifications of nursery routines in most institutions. However, it will still be possible, by paying more attention to the cry, to reduce the amount due to unknown reasons. This will mean more individualization in the care of each baby.

The actual amount of daily nursing care was 1.9 hours for each baby this year in contrast to the meager 0.7 hours last year. Considering the helpless condition of a newly born baby, we feel that increasing the amount of effective nursing care available to these infants is justified. We seem to be approaching the optimum, but still further changes will decrease the crying.

SUMMARY

A study of the crying in the nursery for newly born babies at one of the hospitals in Rochester, Minnesota, was done after making more nursing care available and individualizing the babies' care. The study was based on data obtained from continuous observation for eight days.

The average amount of crying for each baby was 55 minutes each day in contrast to 113.2 minutes during the study in 1944. The average number of times each baby cried daily was eighteen, of which 5.7 were prolonged spells, that is, crying lasted more than 3 minutes.

Hunger led the list of causes for crying, but unknown reasons was close behind. Wet diaper, soiled diaper, and vomiting remain in that order as minor causes of crying.

The actual amount of nursing care given each baby daily was 1.9 hours in contrast to 0.7 hours during the study in 1944. This was 43.1 per cent of the available nursing time.

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INTRACISTERNAL PENICILLIN

OBSERVATIONS OF ITS EFFECT ON DOGS

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THE reading of the article, "Intraventricular Penicillin: A Note of Warning,"¹ having aroused interest in the possible deleterious effect of penicillin on the central nervous system, it was decided to observe the effect on dogs of intracisternal injections of the drug, and the following experiment was begun. Shortly afterward, Walker and Johnson² published further work along the same lines, and this report constitutes a corroboration of their findings and the recording of certain additional observations not included in their article.

Dogs were lightly anesthetized with intravenous pentothal sodium, and observing the usual aseptic precautions, intracisternal taps were executed. These were done at twenty-four to forty-eight hour intervals, and on each occasion, instillation of the test solution was preceded by withdrawal of a corresponding volume of cerebrospinal fluid. Reactions following each instillation were noted, and the cisternal fluid was examined.

The control experiments were performed on six dogs, average weight 23.5 pounds. Injections were of 5 c.c. sterile normal saline solution, each animal receiving from five to seven injections. From a total of thirty-eight injections, five instances of brief stiffening of the extremities and sometimes of the neck also, lasting for only a few minutes, were noted in three dogs. No convulsions occurred, nor were other reactions observed. The cerebrospinal fluid showed only irregular slight increases in leucocyte content, with the predominant cell being of the mononuclear variety. Higher rises on a few occasions may have been due to infection and were concurrent with the only positive Pandy reactions and sugar content alterations seen in the series. Two of the dogs were sacrificed and autopsies were done. Histologic changes were not observed in the brains, cervical cords, or meninges.

The second group of animals consisted of six dogs, average weight 20.3 pounds. Instillations were of 5,000 units of penicillin in 1 c.c. sterile normal saline solution. One dog received five such injections; another, eight; a third, nine; and the remaining three, ten each. From a total of fifty-two injections, there occurred a total of ten (19.2 per cent) convulsive reactions of which six were mild (e.g., facial twitchings, snapping of jaws, frothing, defecation), and the remaining four, minimal (e.g., facial twitchings with or without frothing). No convulsions occurred with the first dose of the drug. Two of the six dogs failed to convulse. The number of leucocytes in the cerebrospinal fluid was

From the Department of Pediatrics, Duke University School of Medicine. Thanks are due to Drs. George O. Boucher, and Keith M. Oliver for assistance in performing these experiments; to Dr. Walter G. Gobbel, Jr., who made the histopathologic observations; to Dr. Wiley D. Forbus, who critically reviewed the microscopie sections; and to Dr. Jay M. Arena for encouragement and helpful suggestions during the course of the work.

again not elevated above that of the control series. No abnormalities were discovered with the Pandy or Benedict reactions. Pathologic sections were not remarkable in two of the dogs, of which one had had convulsions, and one had not. Another dog showed a minimal meningitis, plus a rather profuse hemorrhage into one of the lateral columns of the cervical cord, in which the red blood cells were accompanied by numerous, small round cells and macrophages, and a few polymorphonuclear leucocytes. A fourth dog showed, in several areas over the cerebral cortex, minimal subarachnoid accumulations of small round cells and polymorphonuclear leucocytes, together with several small areas of hemorrhage into the cervical cord. The fifth dog showed a minimal inflammatory process involving the pia-arachnoid, together with a hemorrhage into the brain substance extending caudad from the rostral part of the medulla. The sixth dog supplied the only instance of an acute purulent meningitis, the process involving the pia-arachnoid, chiefly over the inferior portion of both temporal lobes, but extending also over the frontal, parietal, and cerebellar lobes, bilaterally. The exudate consisted in large numbers of polymorphonuclear leucocytes, among which were many eosinophiles and some mononuclear cells. No bacteria were demonstrated in the sections.

The third group of dogs consisted of four animals selected, after a rest period of five days, from the control group. Average weight was 23.5 pounds, and individual states of health appeared excellent. One dog received eight injections; the other three dogs received nine injections each of 10,000 units of penicillin in 2 c.c. sterile normal saline solution. From a total of thirty-five injections, severe convulsions (although not so violent as those noted in the fourth group) were observed in seven instances, a moderately severe convulsion in one instance, and mild convulsions in sixteen instances, for a total incidence of twenty-four reactions, or 68.6 per cent. Again no convulsions occurred with the first dose of the drug. No dog in the group failed to convulse. The cerebrospinal fluid did not differ, significantly, in leucocyte content from that of the control series, nor were globulin and sugar contents appreciably altered. Post-mortem studies revealed no lesions in three of the dogs, but in the fourth, a small area was found in the cerebral cortex in which there was moderate perivascular cuffing by round cells, together with a few scattered cells of similar type in the subarachnoid space.

The fourth group consisted of only two dogs, one of which received two injections of 100,000 units of penicillin in 5 c.c. sterile normal saline solution. The other dog received similar doses four times in the lumbar region, the fifth dose being administered by the cisternal route. Since no cerebrospinal fluid could be obtained at the time of any of the lumbar injections, it is doubtful that the drug reached the subarachnoid space in these instances. Although anesthetized, both dogs whimpered as if in pain during intracisternal instillation of the penicillin. Severe convulsions, beginning two minutes after injection, occurred after the second injection in the first dog; in the second dog, no reaction followed four lumbar (intramuscular?) injections of the drug, but convulsions, equally severe, began seven minutes after the first intracisternal injection. Convulsions in both dogs began as facial twitchings, followed in rapid progression

by generalized seizures, consisting of violent clonic movements of the extremities and neck, with forceful striking of the head against the concrete floor, snapping of the jaws, excessive salivation, defecation, labored respirations, cyanosis, and apparent blindness. Death followed the convulsions of the first dog, while the other remained moribund for seventy-two hours and was sacrificed. Cerebrospinal fluid studies were too inadequate to permit conclusions to be drawn. Post-mortem examination of the first dog revealed only moderate congestion of the meningeal vessels. Numerous small infarcts were found, however, throughout the brain and cervical cord of the second dog, especially in the medulla and cervical cord, and in these areas were noted a few small round cells, some of them forming a perivascular cuff. There were, in addition, several subarachnoid accumulations, all minimal, of small round cells, plasma cells, and occasional polymorphonuclear leucocytes.

It was noted that all convulsions, regardless of degree of severity, were preceded by a sort of aura in which the dog appeared preoccupied, stared vacantly, lowered his head, and if disturbed, snapped irritably at the aggressor. During those convulsions sufficiently mild to permit maintenance of equilibrium, vision seemed seriously impaired, so that the dogs collided repeatedly with obstacles in their paths. Sight was restored at the end of the convulsion. A period of extreme apprehension and excitability followed most of the convulsions.

CONCLUSIONS

1. Convulsive reactions to intracisternally administered commercial penicillin were observed in dogs, corroborating reports in the recent literature.
2. Histopathologic studies revealed several instances of hemorrhage into the brain substance, with multiple cortical infarcts in one animal. Also noted, was the occurrence in several dogs of minimal meningitis and perivascular round cell cuffing, as well as one instance of acute purulent meningitis.

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GALACTEMIA

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IN 1917, Goppert¹ described a chronically ill child, with a background of liver disease, who was found unable to tolerate galactose and who thrived only when lactose was removed from his diet. In 1935, Mason and Turner² presented a similar case with extensive carbohydrate studies, and more recently Norman and Fashena³ presented a third. Two more cases hitherto unpublished are in the records of the Harriet Lane Home.⁴ A sixth case has recently been published by Mellinkoff and associates⁵ and a seventh case has been reported recently by Bruck and Rapoport.⁶ We shall describe two additional cases in which this condition occurred. The metabolic anomaly found in these children is undoubtedly rare, but it probably occurs oftener than the paucity of records would suggest. A composite picture of this symptom complex includes (1) athrepsia with insatiable hunger, (2) hepatomegaly, (3) lamellar cataracts, (4) galactosuria, and (5) mental retardation. All but the last are probably constant findings. This condition should be considered as a possible diagnosis whenever hepatomegaly, inanition, cataract, and melituria are encountered in young infants. The diagnosis is readily made if the reducing substances in the urine are properly identified. We present two patients in whom these features were found. These cases will be discussed with regard to present concepts of galactose metabolism and of galactose cataractogenesis which are now briefly reviewed.

Endogenous galactose occurs in certain constituents of nerve tissue, the galactolipids or cerebroside. It is not known how they function and how necessary they are, but some writers consider them essential, and they argue teleologically that galactose exists in milk so that the nursling may use its available galactose in the formation of nerve tissue, especially in the myelinization which occurs at a rapid rate in the first six weeks of life.⁷ It is possible that the body can synthesize galactose for this purpose. Certainly galactose is synthesized in the lactating breast.⁸

Exogenous galactose is ingested chiefly or entirely as one fraction of the lactose molecule in milk. Absorption of galactose takes place in the small intestine. This process is thought to consist of a phosphorylation of the sugar in the intestinal mucosa, which increases the gradient of diffusion of the sugar into the mucosal cells. This is an active physiologic process as it is with glucose and not the mere physical diffusion by which all other monosaccharides enter the portal circulation. The absorption of galactose is somewhat more rapid than the absorption of glucose. The process is limited quantitatively and the simultaneous absorption of one sugar inhibits to some extent the absorption of the other.⁹

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The galactose proceeds to the liver where it undergoes conversion to glucose and to glycogen. The intermediate steps by which this occurs are not fully known. Glucose -1- phosphate and galactose -1- phosphate are both present in the liver during galactose assimilation, although there is no progressive accumulation of the latter phosphate. There is an increase in reducing phosphoric esters, particularly glucose -6- phosphate. The increased glucose content of the liver during galactose assimilation would seem to demonstrate the conversion of galactose to glucose. All of the above-mentioned substances probably participate in this conversion.¹⁰ It is doubtful whether glycogen formation takes place only after the galactose has become converted to glucose; for the glycogen thus formed varies in certain respects from that formed directly from glucose: the molecular size of the former corresponds to 18 glucose units, whereas that of the latter corresponds to 12 glucose units, and, once formed, the former undergoes glycogenolysis more slowly than the latter.¹¹ An enzyme system in the liver for the conversion of galactose into glucose and glycogen has been inferred but not demonstrated. The normal liver can convert galactose at a certain rate; the galactose tolerance test has thus become used as a measure of liver function.

The galactose not assimilated by the liver remains in the blood and can be demonstrated in the systemic circulation. Its fate thereafter, apart from excretion by the kidneys, is disputed. It has been shown that a frog spinal cord can metabolize galactose faster than glucose when it is at rest and slower than glucose when it is being stimulated.⁸ Galactose can be utilized by diabetics and has an antiketogenic effect.^{12, 13} There is a difference between the arterial and venous levels of galactose during galactose assimilation.⁸ Finally the hepatectomized dog is able to metabolize certain amounts of galactose.¹⁴ These facts suggest the possibility of extrahepatic utilization of galactose; however, this probably does not occur on any large scale. Galactose produces a steeper and higher rise in the respiratory quotient than does glucose.¹⁴ This suggests that, either at the hepatic level or in the tissues, galactose is utilized apart from being converted into glucose. The galactose remaining in the arterial blood is excreted by the kidneys even at a low blood concentration so that there is no appreciable renal threshold for galactose. It has been found that the renal tubules of the dog absorb about 40 per cent of the galactose that appears in the glomerular filtrate.¹⁵

The interest in the relation between galactose and cataract formation began in 1935, with the accidental finding in an unrelated experiment that cataract developed in all rats that received a 70 per cent lactose ration.¹⁶ Three years earlier Kirby and associates¹⁷ had made the important observation that galactose had a direct toxic effect on lens epithelium cultivated *in vitro*. Feeding a high galactose ration became the standard method of producing cataract in experimental animals.

The changes in the lens occurring as a result of galactose administration are as follows: The earliest microscopic changes involve first the cortical fibers near the equator, then the capsular epithelium and finally the nucleus. Macroscopically there is first ciliary hyperemia, then the appearance of fluid droplets in the peripheral lens tissue, and eventually opacity sets in under the capsule

and in the central nuclear portion.^{18, 19} Some workers^{20, 21} found senile suture lines. The permeability of the lens capsule has been variously found increased²¹ and decreased.²² The precise changes vary with the species and age of the animal utilized. For example, young albino rats develop nuclear cataract and older rats develop cortical cataract.²³ On withdrawing galactose the cortical opacity may clear, but nuclear opacity remains.²⁴

The chemical changes in the lens following galactose administration have also been studied. There is an increase in total ash with more sodium, calcium, sulfate, and carbonate, but less potassium, phosphate, and chlorine. The water content increases. The anions increase more than the cations.²⁵ The organic changes, however, seem to reflect more closely the essential disturbance. Galactose causes a loss of glutathione, cystin, and vitamin C from the lens; the reduction in the sulfhydryl and vitamin C content precedes any sign of cataract.²⁶ The electrical potential in young rat lenses rises in the central portion, a phenomenon which accompanies loss of oxidation-reduction systems and a decrease of metabolic activity.²⁷ It may be noted that many of these changes, such as the rapid development of senile suture lines, the type of mineral content change, the loss of sulfhydryls, and the rise in electrical potentials, are manifestations of tissue senescence and death and are similar to what occurs in senile cataract. It has not been demonstrated that any of these changes are specific for galactose-produced cataract. In other words, galactose poisons the lens, thus confirming the original *in vitro* observation by Kirby and associates.¹⁷ There is no reason to believe that any of these changes explain the action of galactose. Thus it might be preferable to think that the sulfhydryl content of the lens has dropped because the lens has been damaged rather than that the lens has been rendered cataractous because of the sulfhydryl loss.

The reputed influence of galactose upon calcium metabolism, plus the well-known incidence of cataract in certain disorders of calcium metabolism, have suggested to some workers²³ that the explanation of galactose cataract may lie near-by. There has been no general agreement upon the numerous theories developed in this field.

*CASE 1.—G. D. This child was first seen when he was 6 months old. He was the second child of young parents in good health; the first child was considered normal. The delivery was at term and not unusual. The baby weighed 7½ pounds at birth; he soon became jaundiced and remained so for two or three weeks. The baby was always considered a feeding problem; he often refused feedings, cried a great deal after meals and before bowel movements, and frequently had a distended abdomen. He did not vomit, however, and only occasionally had loose watery stools. Frequent formula changes reflected these difficulties: he had been nursed for the first three weeks and was then given various formulas of evaporated milk, cow's milk, and condensed milk. Because of his failure to thrive, he was brought to Montreal and admitted to the Children's Memorial Hospital on April 25, 1939.

Physical examination revealed an irritable, emaciated, male infant who weighed 8½ pounds, only one pound above birth weight, and who seemed to be younger than his age of 6 months. There was a marked lack of muscle tone. The eyes showed bilateral cataracts with dense central opacities. Nothing unusual was found on examination of the upper respiratory tract or the thorax. The liver was enlarged, the edge reaching below the umbilical level. The tip of the spleen was just palpable.

*Patient on the service of Dr. Alan Ross, presented here with his kind permission.

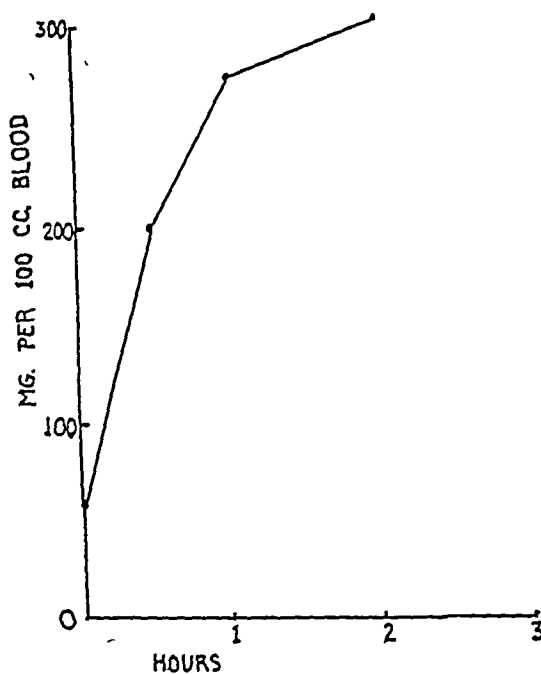


Fig. 1.—Total blood sugar values following ingestion of 1.75 Gm. of glucose per kilogram of body weight. (G. D. May 2, 1939.)

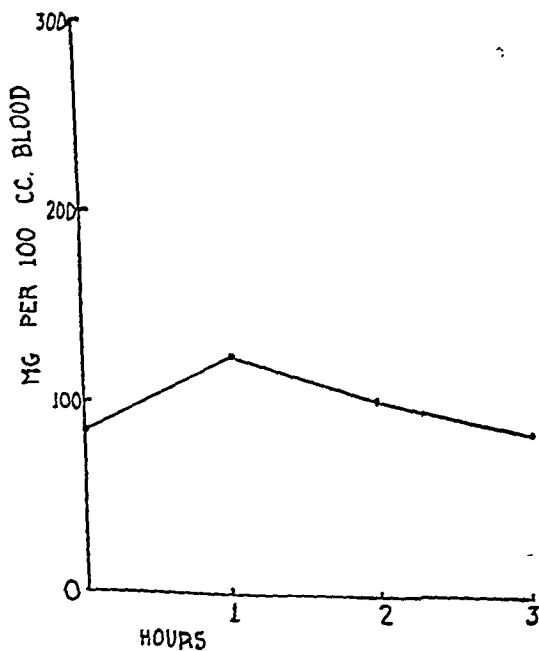


Fig. 2.—Total blood sugar values following ingestion of 1.75 Gm. of glucose per kilogram of body weight. (G. D. March 15, 1940.)

The laboratory findings were the following: The blood Wassermann and Mantoux tests were negative. The red cell count was 4.5 million, the hemoglobin, 14.3 Gm. per 100 c.c., and the white cell count, 23,900. Specimens of urine showed albumin in amounts varying from 75 to 400 mg. per cent and occasional leucocytes and hyaline casts on microscopic examination. No bile, urobilin, or acetone was found. The most arresting laboratory finding was the urinary sugar, which ranged from 1 to 3 per cent. The fasting blood sugar was 59 mg. per cent.

The indirect Van den Bergh was 3.0 units; the direct, 0 units. The blood calcium was 10.2 mg. per cent, the phosphorus, 4.8 mg. per cent. There were 30 mg. per cent of non-protein nitrogen in the blood plasma. There were 5.6 Gm. per 100 c.c. of total protein in the plasma, of which 4.62 Gm. per 100 c.c. were albumin, 0.52 Gm. per 100 c.c. globulin, and 0.46 Gm. per 100 c.c. fibrinogen. The blood cholesterol was 125 mg. per cent. Roentgenographic examinations of the chest and skull revealed nothing remarkable. The bones were generally decalcified.

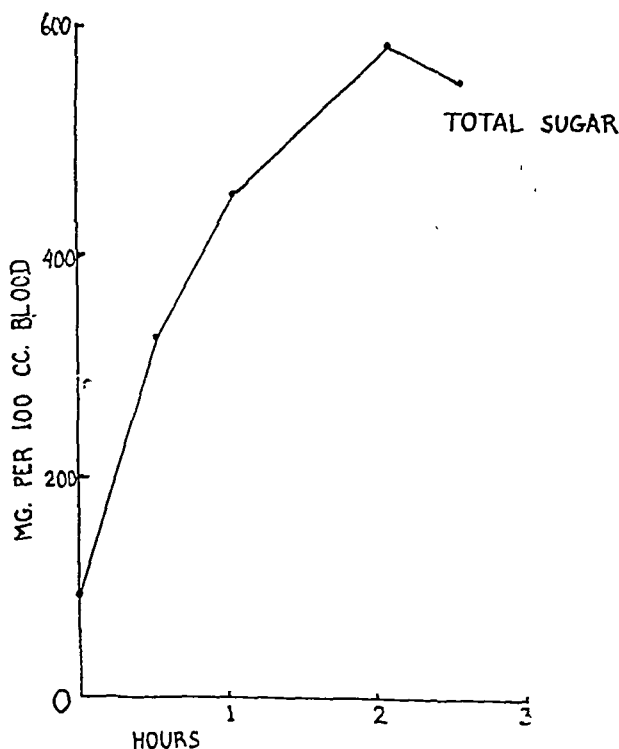


Fig. 3.—Total blood sugar values following ingestion of 1.75 Gm. of galactose per kilogram of body weight. (G. D. May 23, 1939.)

The melituria raised the question of diabetes. But when repeated examination of the baby's glucose tolerance (Figs. 1 and 2) failed to confirm this diagnosis, it was suggested that this case might be similar to the case reported by Mason and Turner.² Identification of the sugar in the urine was therefore undertaken. When subjected to the action of baker's yeast, the sugar did not ferment. The reducing power of this sugar was not increased by acid hydrolysis; this ruled out the presence of disaccharides. Osazone crystals were then prepared which were identical with those of galactosazone. Mucic acid crystals identical with those prepared from galactose were obtained.

While the identity of the reducing substance in the urine was thus being established as galactose, a striking defect in the child's galactose tolerance was demonstrated by a curve in which the blood galactose reached a peak of 588 mg. per cent and was still above 500 mg. per cent two and one half hours after the ingestion of galactose (Fig. 3). This hypergalactosemia and the galactosuria were accepted as proof of the baby's intolerance to galactose. Studies of the child's carbohydrate metabolism, carried out along the lines followed by Mason and Turner,² are reported in detail.

Course.—On the basis of the diagnosis of galactose intolerance, the child was given a lactose free diet, consisting of cereal, vegetable, egg yolk, and a formula made from Sobee (a proprietary soybean flour) and corn syrup. The sugar and albumin were found to have disappeared from the urine three days later. The child then began to thrive; and in spite of several attacks of otitis media requiring sulfonamide therapy and numerous myringotomies, he gained four pounds in the next three months. He continued to do well in spite of mumps, chicken pox, and further respiratory infections, including pneumonia at least twice. He spent several months in a convalescent hospital, and two weeks in a contagious disease hospital when suspected of having pertussis. When the child returned to the Children's Memorial Hospital at 14 months of age, it was found that his liver was a little smaller, the cataracts were possibly less dense, and the Van den Bergh had become normal. The bones were still quite decalcified, although the fontanel had closed. When 15 months old, the child weighed 20 pounds, had five teeth, but was still unable to sit alone. He could apparently see moving objects and would reach for them. The cataracts were now definitely less dense than on admission. The liver was only 1 cm. below the costal margin. The child was discharged at the age of 20 months on a lactose-free diet, consisting of egg, meat, fruit, vegetables, cereals, and gelatin puddings made without milk, with a supplement of dicalcium phosphate and adequate vitamins.

When 6½ years old, the boy was readmitted to the Children's Memorial Hospital on May 31, 1945, for observation and for treatment of the cataracts which had persisted. He had adhered strictly to a milk-free diet in the interval. He had remained well until he contracted pertussis in December, 1944. In March 1945, he developed a choreiform disturbance, apparently mild, which subsided in a few weeks. His development had been slow. He sat alone soon after leaving the hospital, at about 20 months of age and began to walk at 27 months of age. He began to talk at a later date and learned slowly. He could not see very well and was not skillful with his hands. He was not considered able to begin school.

Physical examination revealed a well nourished active boy 6½ years of age, who weighed 48 pounds. Lamellar cataracts with a few peripheral striae were present. The edge of the liver could be felt 2 cm. below the costal margin. It was difficult to assess the child's intelligence because of the impairment of vision and the presence of a speech defect, but he was considered somewhat mentally retarded.

The cataracts were needled and the lenses evacuated.

Examination of the blood chemistry yielded the following information: the bilirubin level was normal, the total protein 7.66 Gm. per 100 c.c. of which 4.00 Gm. were albumin and 3.61 Gm. were globulin. The prothrombin time was within normal limits and a cephalin flocculation test was normal. The long bones were x-rayed and found to be normal. The galactose tolerance was re-examined (Fig. 7) and found to have improved somewhat since the last examination five years earlier (Fig. 4).

Carbohydrate Studies.—In the first glucose tolerance test (Fig. 1) a curve not unlike that of diabetes mellitus was obtained, though the low fasting level was unusual. The latter, coupled with the massive hepatomegaly, suggested a glycogen storage disease; but an adequate elevation of blood sugar in response to an injection of epinephrine ruled this out, and confirmed the initial objection that the hyperglycemia in the tolerance test and the absence of ketosis were incompatible with von Gierke's disease. Subsequent glucose tolerance curves demonstrated an excessive rise in the blood sugar but a fairly adequate recovery to within normal limits. These findings were considered characteristic of a state of starvation: the

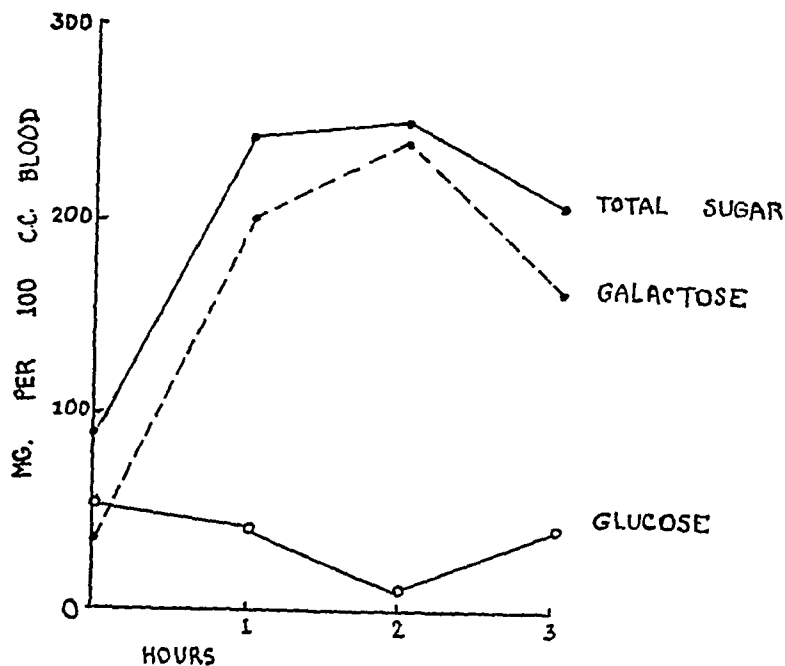


Fig. 4.—Values for total blood sugar, galactose, and glucose following ingestion of 1.75 Gm. of galactose per kilogram of body weight. (G. D. Jan. 30, 1940.)

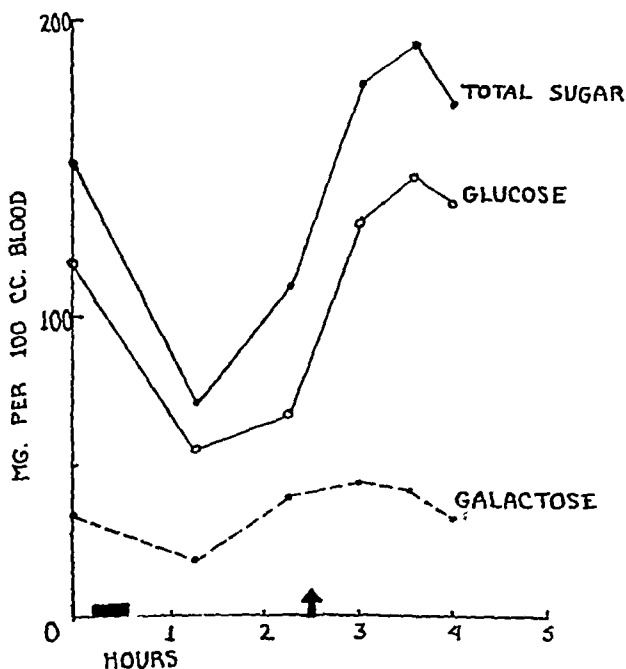


Fig. 5.—Values for total blood sugar, galactose, and glucose. Each heavy line along the abscissa represents the ingestion of a meal containing 200 c.c. of milk and 10 Gm. of lactose. The arrow indicates the subcutaneous administration of 5 minims of a 1:1,000 solution of epinephrine. (G. D. April 24, 1940.)

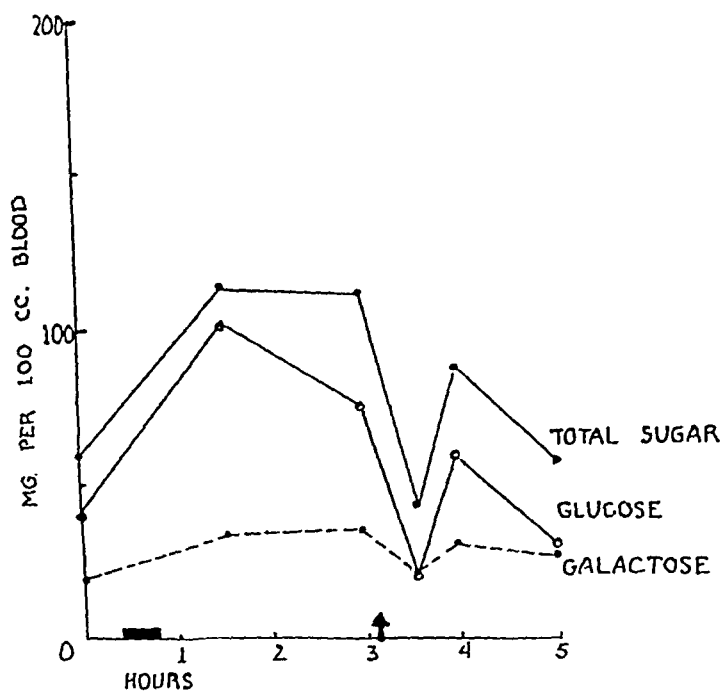


Fig. 6.—Values for total blood sugar, galactose, and glucose. The arrow indicates the subcutaneous administration of 5 units of insulin. The meal contained 200 c.c. of milk and 10 Gm. of lactose. (G. D. April 25, 1940.)

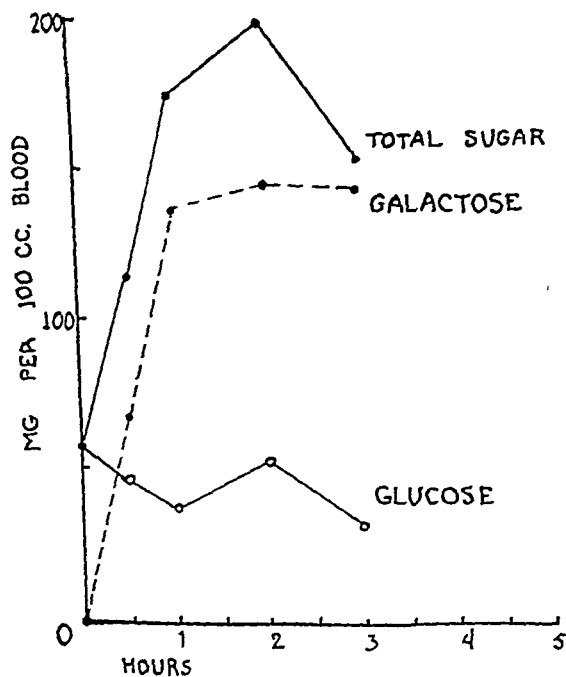


Fig. 7.—Values for total blood sugar, galactose, and glucose following ingestion of 1.75 Gm. of galactose per kilogram of body weight. (G. D. June 5, 1945.)

child's nutritional status was remaining unsatisfactory and he was still eating poorly. This conclusion was justified by a normal glucose curve obtained ten months later when good nutrition had been established (Fig 2).

The identification of the urinary sugar as galactose and the demonstration of greatly impaired galactose tolerance (Fig 3) showed that we were dealing with a case of galactemia. A second galactose tolerance test eight months later, the patient having been on a lactose free diet in this interval and now in greatly improved health, appeared to show that his tolerance for galactose had increased somewhat, although it remained well below normal. The blood sugar values at this examination (Fig 4) were fractionated by fermentation with yeast. Here a depression of the level of blood glucose accompanied the peak of the curve of the galactose fraction. This was more marked than the corresponding finding by Mason and Turner,² and much greater than the depression of blood glucose which galactose can apparently cause in a normal person.⁷ Epinephrine raised the level of blood galactose a negligible amount, while it had the usual effect on blood glucose (Fig 5). Insulin lowered the level of blood galactose slightly, while producing the usual depression of blood glucose (Fig 6). We did not observe the elevation of blood galactose produced by insulin in Mason and Turner's case, however, the first blood determination was unfortunately made as late as one half hour after the injection of insulin, so that any earlier rise would have been missed.

When the boy was readmitted five years later, the galactose tolerance was examined again (Fig 7). It had improved, the peak value for blood galactose was found to be 146 mg per cent as compared with 240 mg per cent on the last examination (Fig. 4).

CASE 2—M. D. This baby was first seen when she was 3½ months old. The first child of healthy young parents, she was delivered at home at full term. She weighed 6 pounds, appeared normal, and did not develop neonatal jaundice. One subcutaneous injection of BCG vaccine was administered soon after birth. The infant did poorly from the beginning; she vomited a considerable part of her intake and had frequent watery stools. She became ill with cough and fever twice in the first three months. Because the grandmother was blind, the mother worried about the baby's eyes and watched them closely, but she noticed nothing unusual until the baby was 3 months old, then she thought she detected cataracts. The baby was admitted to the Children's Memorial Hospital on Sept. 25, 1944, at the age of 3½ months, having gained only 12 ounces above birth weight.

Physical examination revealed a pale, marantic, and irritable infant, who was poorly nourished and developed and weighed 6 pounds, 12 ounces. The heart and lungs seemed normal. The upper respiratory tract was not remarkable though there was a small amount of nasal discharge and a somewhat dull left eardrum. The abdomen was prominent, due evidently to the great size of the liver which reached almost to the iliac crest and extended 3 cm below the costal margin in the left midclavicular line. It had a smooth surface and a hard edge. Bilateral pinpoint cataracts were present.

The laboratory findings were the following. There was a moderate anemia, with 8 Gm of hemoglobin per 100 cc of blood. The leucocyte count and differential were normal for the age. The blood Wassermann was negative, so was the Mantoux test, although the BCG vaccination had been done only three months earlier. A routine admission urinalysis disclosed a sugar content of 2 per cent. It was then suggested that this child, with her hepatomegaly, cataract, and melituria, might prove to be another case of galactemia.

Identification of the reducing substance in the urine was accordingly carried out. Baker's yeast did not ferment this substance, which gave a positive mucic acid test and yielded galactosazone crystals. It was therefore concluded that the sugar in the urine was galactose. The galactose tolerance test (Fig 8) supported a diagnosis of galactemia. Further studies of the child's carbohydrate metabolism were undertaken and are described.

The remainder of the urinary findings were a mild albuminuria of 20 mg per cent, occasional red and white blood cells, and granular casts, acetone and bile were absent. On the day after admission a lumbar puncture was done because of the extreme irritability and

*Patient referred by Dr. Abel Lux.

the presence of a questionably full fontanel. This yielded spinal fluid under normal pressure, with no pleocytosis, a negative Pandy, and protein and chlorides within normal limits. The spinal fluid sugar was 161 mg. per cent, more than twice the normal value. (How much of this consisted of galactose was, unfortunately, not determined.) The total level of bilirubin in the plasma was 0.435 mg. per cent. The blood cholesterol was 91.9 mg. per cent. The total plasma proteins were 4.44 Gm. per 100 c.c., 3.90 of which were albumin and 0.54 globulin. Roentgenographs of the long bones demonstrated no decalcification.

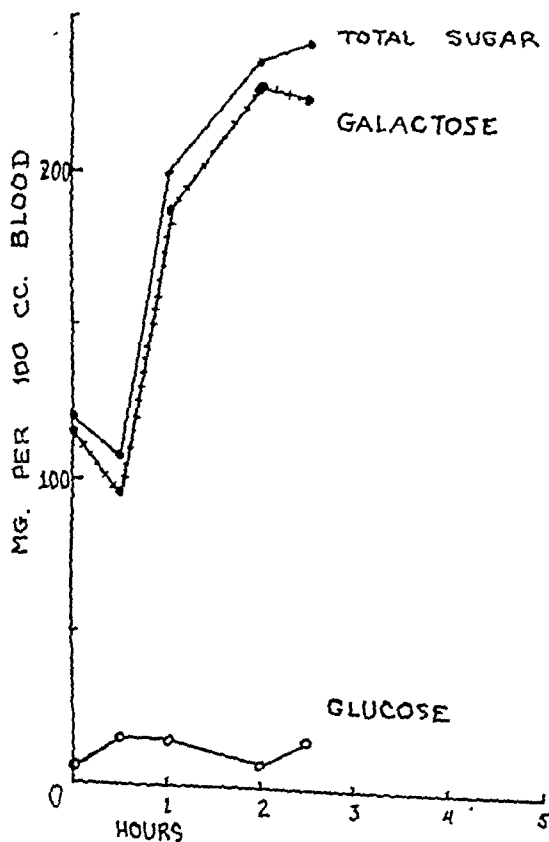


Fig. 8.—Values for total blood sugar, galactose, and glucose following ingestion of 1.75 Gm of galactose per kilogram of body weight. (M. D. Oct. 6, 1944.)

Course.—Lactose was removed from the baby's diet three days after admission to hospital. At first she was fed bananas, egg yolk, Pablum, and a soybean flour formula. Because the latter was taken poorly it was replaced by a more acceptable suspension of washed milk curds in Ringer's solution sweetened with corn syrup. Sugar and albumin disappeared from the urine one week after the new regime was begun. Nevertheless the baby did not do well for some time afterwards. She had respiratory infections, particularly otitis media, accompanied by fever, diarrhea, and dehydration, requiring intensive chemotherapy, and the parental administration of fluids, including plasma and whole blood. When placed on a frame for the purpose of collecting a 24-hour specimen of urine, the baby rapidly developed decubitus ulcers on the thighs. These became deep and undermined and did not heal for several weeks. The baby's condition gradually improved, and she was discharged at the age of 5 months, weighing 8 pounds. The baby thrived at home on the same diet given in the hospital, to which were soon added puréed vegetables, beef, and liver. She had recurrent upper respiratory infection and otitis media, to which she remained very susceptible.

At 9½ months of age she was readmitted for further study. At this time she weighed 16 pounds, appeared very well nourished, had good color, could stand with support, and seemed to see quite well in spite of the cataracts which had perhaps regressed slightly, now appearing restricted to a 1.5 mm. central anterior opacity. The liver was somewhat smaller than on the first admission but still extended 5 cm. below the costal margin. Radiographs of the long bones still showed no decalcification. A prothrombin time of 17 seconds and a negative cephalin flocculation test demonstrated unimpaired liver function. The urinalysis was negative. There was no essential change in the blood chemistry, except that the total plasma protein had risen to 6.66 Gm. per 100 c.c. with the globulin dropping to 0.10 Gm. per 100 c.c., even lower than on the first examination. However, at one year of age the serum globulin had reached 1.62 Gm. per 100 c.c., a normal figure.

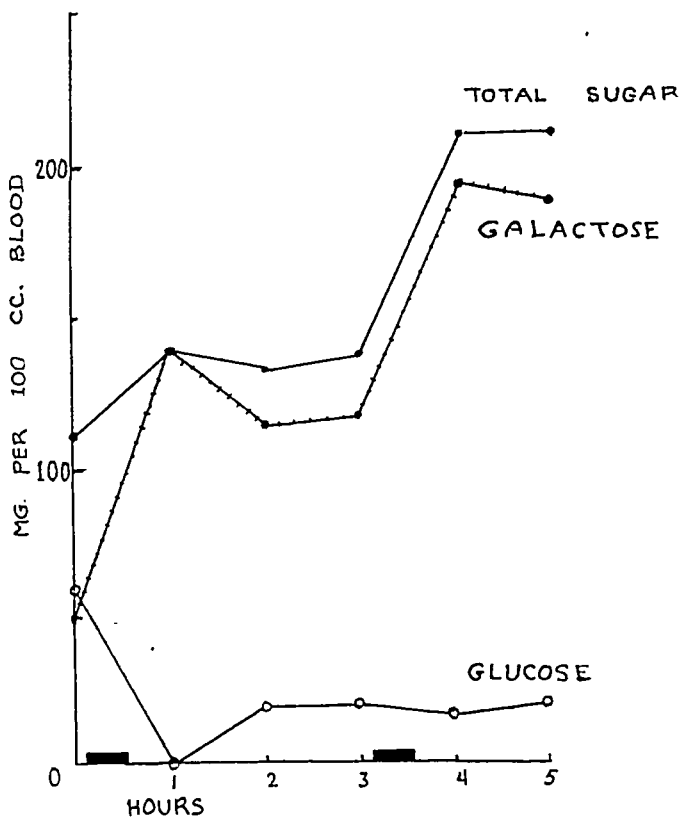


Fig. 9.—Values for total blood sugar, galactose, and glucose. Each heavy line along the abscissa represents the ingestion of a meal containing 200 c.c. of milk and 10 Gm. of lactose. (M. D. Oct. 17, 1944.)

Carbohydrate Studies.—A galactose tolerance test was carried out (Fig. 8). The greatly impaired tolerance shown confirmed the diagnosis of galactemia. The sugars were fractionated according to the method of MacLagan.²⁸ Here one noted an even greater depression of the blood glucose than was observed in Case 1. The high fasting level of galactose was evidently due to the fact that the baby received galactose test meals on the two previous days in technically unsuccessful attempts to study her tolerance and had not yet excreted all this galactose. The meaning of the initial drop in the galactose level preceding the rise is obscure. It was then demonstrated that when the child was given an ordinary diet containing milk, the blood was never free of galactose and always had a low glucose content (Fig. 9).

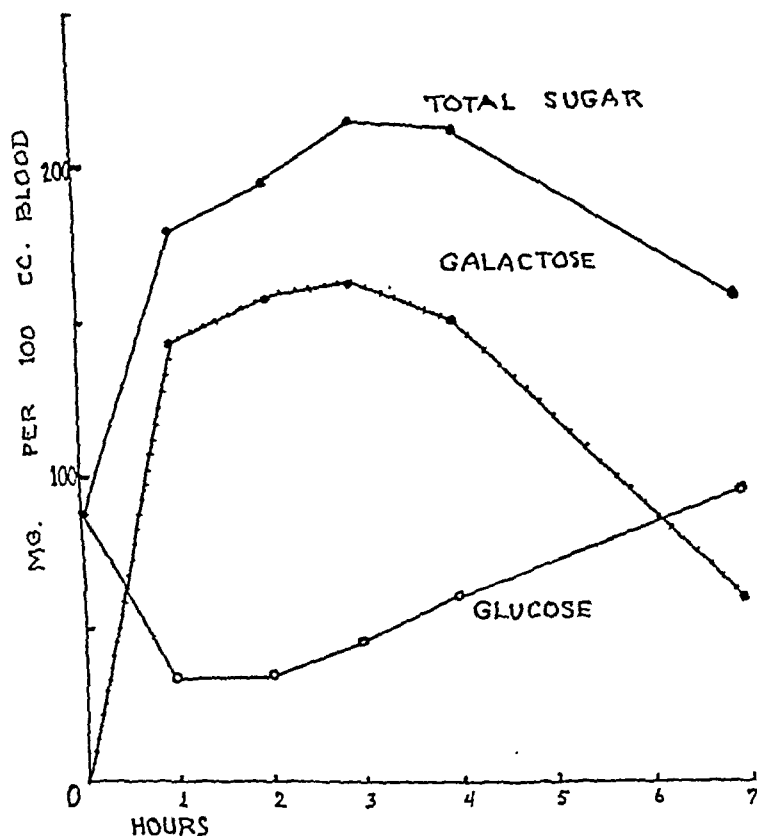


Fig. 10.—Values for total blood sugar, galactose, and glucose following ingestion of 1.75 Gm. galactose per kilogram of body weight. (M. D. April 10, 1945.)

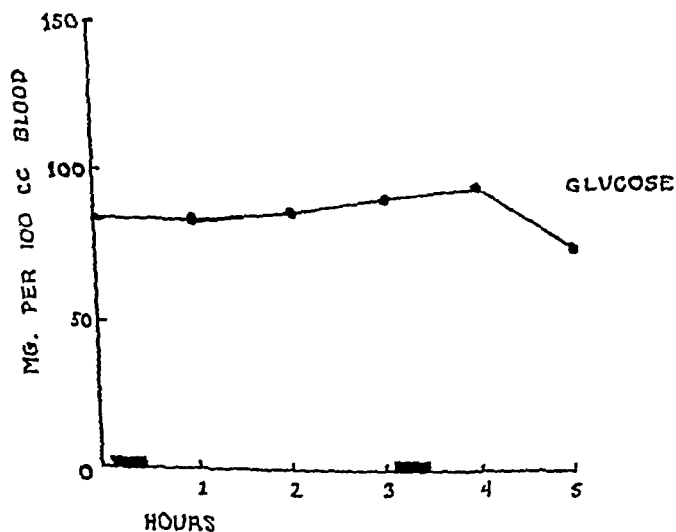


Fig. 11.—Values for total blood sugar. Each heavy line along the abscissa represents the ingestion of a lactose-free meal. The total blood sugar in these determinations consisted entirely of glucose, the presence of galactose having been excluded by fermentation. (M. D. May 25, 1945.)

On the second admission, four and one-half months later, the galactose tolerance test was substantially unchanged (Fig. 10). At this examination, the blood sugars were followed for seven hours after the ingestion of galactose; the galactose then having dropped to 60 mg. per cent, the blood glucose was mobilized to a level slightly higher than the fasting level. The level of blood glucose during the course of a day when the child received a lactose-free diet was then followed as a control to Fig. 9 (Fig. 11). This level proved to be significantly higher than when the child was receiving lactose. The glucose tolerance test was then shown to be within normal limits with glucose administered both orally and intravenously.²⁹ A quantity of galactose (0.2 Gm. per kilogram), calculated to raise the blood galactose to a level corresponding to that reached when milk was drunk, was then administered intravenously immediately preceding an oral glucose tolerance test, and later, preceding an intravenous glucose tolerance test. The intention was to find out which curve would be more profoundly depressed. The oral glucose curve was perhaps more affected than the intravenous glucose curve, but the point cannot be considered solidly established.

COMMENT

Two athreptic infants with hepatomegaly and cataracts were found to excrete a reducing substance in the urine. This reducing substance was identified as galactose. Feeding these children a lactose-free diet eliminated the galactosuria and permitted them to thrive at a satisfactory rate.

Usage thus far has labeled the disease with the name of galactemia, which we believe is not adequately connotative. Galactemia is not present when lactose is absent from the diet, but the metabolic error is always present. This error is the inability of the individual to metabolize galactose. Galactose cannot be utilized by conversion into glycogen but is apparently stored as such in the various organs and circulates as such in the blood stream whence it is excreted through the kidneys unchanged. A suitable name for such a disease would be galactose diabetes, just as diabetes mellitus indicates glucose diabetes. Each name should connote a train of symptoms and events characteristic of the respective metabolic disorder.

DISCUSSION

Galactose diabetes as seen in infants usually presents striking findings which should offer no difficulties in diagnosis. There is always failure to thrive and frequently intense hunger. Not only is lactose not utilized, but there is also good reason to believe that impediments to the utilization of glycogen exist at the same time and explain the hepatomegaly which is marked until lactose is removed from the diet. The tissues are saturated with galactose and the blood level for sugar, consisting chiefly of galactose, is high, and it would appear that the stimulus to glycogenolysis is wanting. Removal of lactose from the diet of such a patient relieves the intense hunger, permits growth, and empties the liver of the excess of stored glycogen. Blood sugar levels fall to normal limits and the sugar in the blood can be shown to be entirely glucose instead of nearly all galactose as when lactose is present in the diet.

The disease should be suspected and sought for whenever an infant manifests extreme hunger with failure to gain though the diet seems adequate, when there is hepatomegaly, cataract, and sluggish healing of damaged skin. Mental retardation was present in one of our cases and in several of those reported.

Fermentation, osazone, and mucic acid tests on the reducing substance in the urine will soon identify it as galactose. Ketosis is not a feature of this disease.

Here are presented two additional patients who could not utilize galactose. Since the important steps in the intermediate metabolism of this sugar, which make it available to the organism, take place in the liver, probably with the assistance of a specific enzyme system as suggested, one may justifiably consider the liver the site of the defect. The evidence implicating the liver is indirect. Massive hepatomegaly is a feature of all the cases reported to date, including our own; this may be only a manifestation of abnormal storage secondary to the primary defect and does not prove liver disease per se; this point will be further discussed. Goppert's¹ patient was icteric for the first eight months of his life. In one of the Baltimore cases, autopsy revealed a malformation of the liver with acinar grouping of the liver cells.³⁰ In the case reported by Mason and Turner,² there was no positive evidence of liver dysfunction. Norman and Fashena³ report some initial delay in bromsulfalein excretion in their case, but no other evidence of hepatic insufficiency. Mellinkoff and associates⁴ report a reversible clinical picture resembling hepatic cirrhosis accompanying the galactemia. Our first patient had jaundice lasting about three weeks in the neonatal period; our second patient showed no liver disturbance. It would appear that this anomaly may occur either as part of the picture of hepatic insufficiency or as a single primary defect of liver function which we assume to be located in the specific enzyme system which converts galactose. We feel that the two cases presented here fall into the latter class.

It is noted that all cases so far reported, except our second case, show an elevation of blood bilirubin; but it is the indirect fraction only which is elevated, the direct being consistently normal. This feature has not hitherto been explained but certainly does not suggest liver damage; it may be correlated with the frequent finding of anemia as evidence of hemolysis. We have no explanation for the occurrence of a hemolytic anemia in this condition.

Mason and Turner² pointed out that the enormous disturbance of nutrition occurring in these children was difficult to account for on a basis of deprivation of the organism of galactose, which amounts to so small a proportion of the expected carbohydrate intake. They postulated that the mechanism for lowering the blood sugar by its storage in the liver as glycogen operates in response to an elevation, not of the blood glucose alone, but of the total blood sugar; but it can act in these cases on glucose only because galactose cannot be converted. This results in an excessively low level of blood glucose. They demonstrated such a continuously low blood glucose in their patient when his diet contained lactose, and they attributed his failure of nutrition to this relative glucose starvation. We are in agreement with this view and have demonstrated in both of our patients a striking hypoglycemia accompanying the hypergalactosemia produced by lactose feedings, the blood glucose reaching zero on one occasion.

If this view of the pathogenesis is correct, the liver enlargement may well be due, as Mason and Turner² suggest, to the excessive formation and storage of glycogen in response to the hypergalactosemia. If so, one would expect the hepatomegaly to disappear when lactose is removed from the diet. In our cases,

the size of the liver decreased rather slowly, remaining somewhat above normal after six months of treatment in our second patient and after five years in our first patient. This suggests that glycogen storage may be only partly to blame. Norman and Fashena³ suggested that storage of something else might occur; fat for instance, or even galactose. The fatty infiltration such as occurs in relative carbohydrate starvation should also disappear more rapidly. It seems entirely possible that some storage of galactose as such does occur, for we found galactose in the urine and blood as late as one week following removal of lactose from the diet. This, of course, might indicate storage in the tissues rather than in the liver; but Norman and Fashena noticed a sudden increase in the size of the liver the day after a large dose of galactose was given. However, galactose storage is equally unsatisfactory as an explanation of the hepatomegaly remaining one year later. The absence of any signs of hepatic insufficiency in the cases under prolonged treatment makes it unlikely that fibrotic changes in the liver may have supervened. Liver biopsy is not available as a means of investigating this problem; for, before good nutrition has been established by a lactose-free regime, it is a hazardous procedure, and after this has been established, it would no longer give the necessary information. Thus the full nature of the hepatomegaly remains unexplained.

It is altogether likely that the blood glucose is depressed in the presence of hypergalactosemia through the mechanism of glycogen formation in the liver, as suggested by Mason and Turner,² and discussed herein. Yet we may consider the possibility of another mechanism, perhaps accessory. The rate of absorption of glucose is slowed by the simultaneous absorption of galactose, the intestinal mucosa being able to accept only a limited load. During the ingestion of milk, the quantity of galactose made available would be too small to affect appreciably the absorption of glucose derived from the other food taken. But since the diffusion gradient of monosaccharide from the mucosal cells into the portal blood must be lessened by a hypergalactosemia, it is reasonable to suppose that the rate of absorption of glucose could be slowed by this means (that is, if it is the level of total sugar, and not merely of glucose, which affects the gradient of glucose from the mucosa into the portal blood as it does from the intestine into the mucosa, a point not yet determined experimentally). Some of the early experiments,⁹ working with a single sugar, showed that one could depress glucose absorption in dogs by raising the glucose concentration of the blood. Verzar,⁹ however, has raised the blood concentration of glucose in rabbits to 520 mg. per cent without affecting the absorption of glucose. In our second patient, the depression of blood glucose by intravenous galatose is relatively greater when glucose is given orally than when it is given intravenously; this finding is compatible with the suggestion that galactosemia interferes with the absorption of glucose from the intestine. Further investigation of this point is required.

Whether we are dealing with blocked absorption of glucose, or solely with hepatic hoarding of glucose with deprivation of the tissues, the net effect of hypergalactosemia is one of glucose starvation. Norman and Fashena³ pointed out that the glucose tolerance curve of their patient was at first similar to a curve obtained during starvation, and demonstrated the gradual return of the

glucose tolerance to normal with treatment. We observed the same phenomenon in our first case. It is possible that this tissue starvation is responsible for such features as the intractable pressure ulcers in our second patient, and the constant finding of albuminuria; although a direct toxic effect of excess galactose in the tissues cannot be excluded.

Mental retardation has been observed in the patients described by Goppert,¹ and Mason and Turner,² and in our first patient. It is not present in the patient described by Norman and Fashena³ and in our second patient. It was notably in the latter two that removal of lactose from the diet was effected early, before the twentieth week of life. This suggests that the mental retardation is not an associated congenital defect, but rather a result of the interference by the galactosemia with the supply of glucose to brain tissue as well as to other body tissues; or perhaps there is a direct toxic effect of excess galactose on brain tissue. There would seem to be no disturbance of myelinization as a result of the therapeutic withdrawal of exogenous galactose, judging from the satisfactory neuromuscular development of our second patient.

Although galactose is not converted into glycogen it seems able to prevent the appearance of hypoglycemic symptoms. In one experiment (Fig. 11) when a milk meal enriched with added lactose was fed, glucose apparently disappeared completely from the circulating blood within one hour and the total blood sugar of about 140 mg. per cent consisted entirely of galactose. Yet no symptoms of hypoglycemia appeared. One patient did, however, have a brief convulsion during the course of a carbohydrate-insulin curve, at a time when the blood glucose was 43 mg. per cent and the galactose 90 mg. per cent. We have no explanation of this to offer. (This curve is not reproduced here because it was incomplete.) This brings up the interesting question of the nature of hypoglycemic reactions. We may assume that galactose can be utilized directly by nerve tissue, perhaps by a mechanism which involves the intermediate metabolism of the cerebroside or lactolipids, and thus protects nerve tissue from damage in periods of glucose depletion.

Certain other findings are difficult to explain. Both of our patients repeatedly showed unusually low values for serum globulin at first, but normal values later. This was not so in the other cases reported. We do not know its significance. The susceptibility of both of these infants to infections may be on this basis. We cannot explain the osteoporosis present in all the reported cases and in one of our cases.

Treatment of these children consists essentially of the withdrawal of milk from their diet. The substitute most commonly used has been a formula prepared from soybean flour, with other foods and vitamins suitable to the age period. The Sobee formula was taken well by our first patient but not by our second. For this reason the simple expedient of using washed milk curds resuspended in Ringer's solution sweetened by corn syrup was successfully tried. Goppert¹ used a similar feeding for his patient. It may be noted that whereas any milk is injurious to these infants, human milk is more so than cow's milk because of its higher lactose content.

It is possible that the galactose tolerance of these children may improve over a period of time. Thus the total blood sugar curve obtained in Case 1 after a galactose test meal reached 588 mg. per cent the first time (Fig. 3) and only 250 mg. per cent seven months later; five years later it reached 200 mg. per cent (Fig. 7). Curves in Case 2 did not change appreciably in six months.

It is of interest to find in one of the first articles by Mitchell and Dodge¹⁶ on galactose cataract, a reference to Mason and Turner's² presentation of a case of galactemia. In view of the infallible production of cataract in experimental animals by the feeding of galactose in quantities sufficient to raise the blood galactose level appreciably, the conclusion may justifiably be drawn that the hypergalactosemia in these children causes the cataract. The objection has been that in both of these cases the cataract has been chiefly nuclear, and nuclear cataract is generally considered to form before the development of the lens nucleus has been completed, that is by the third month of fetal life. A normal galactose tolerance test on the mother of the patient in Case 2 ruled out the exposure of this infant to a high concentration of blood galactose during fetal life. This mother's story is that the cataract was not present at birth. Finally the production of nuclear cataract in young rats, by high blood levels of galactose in postnatal life, is at least strong, suggestive evidence that cataract may occur in this way in human young. It is certainly significant that the incidence of cataract in cases of galactemia has been to date at least 50 per cent.

The experimental finding that galactose-produced cataract regressed in part, on withdrawal of galactose,²⁴ is of interest here. The patient described by Mason and Turner had cataracts and has undergone operation for them.³¹ The cataracts exhibited by a patient with galactosemia studied by Bruck and Rapoport⁶ resolved after galactose was removed from the diet. Our first patient's cataracts regressed only slightly over a six-year period of observation, at the end of which time operation was performed. Our second patient's cataracts have regressed very little after nine months of observation.

SUMMARY AND CONCLUSIONS

1. Two infants in whom occurred the syndrome of hepatomegaly, inanition, cataract, galactosuria, and galactosemia are presented.
2. This anomaly of galactose metabolism is discussed.
3. The cataract in this condition is related to experimentally produced galactose cataract, the pathogenesis of which is reviewed.
4. Therapeutic control of this condition is readily effected by a lactose-free diet.

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IMMUNIZATION WITH TETANUS TOXOID

THE PERSISTENCE OF ANTITOXIN AND THE EFFECT OF STIMULATING DOSES OF ALUM-PRECIPITATED TETANUS TOXOID AFTER A FIVE-YEAR PERIOD

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ACTIVE immunization against tetanus is now recognized as a routine procedure in pediatric practice. The antitoxin response to two injections of tetanus toxoid alone or in combination with diphtheria toxoid has been most gratifying. However, few data are given on the persistence of antitoxin in immunized individuals and the antitoxin response after several years to the injection of varying amounts of tetanus toxoid.

In 1936, we reported¹ the serum antitoxin content in ninety-four children following immunization with two doses of 1 c.c. each of alum-precipitated tetanus toxoid with an interval of seventy-three days. The toxoid used had a minimum toxicity of 15,000 minimum lethal doses per cubic centimeter. Serum antitoxin levels were determined forty-five days after the first injection and fifty-four days after the second injection. The methods of testing for serum antitoxin have been previously described.¹ The results of this study are summarized in Table I. After the first injection, 16.3 per cent of the children had an antitoxin level of 0.1 unit per cubic centimeter⁴ and after the second injection all children had 0.1 or more units per cubic centimeter, while the majority had from 0.25 to 1 unit of antitoxin per cubic centimeter of serum. These data are in agreement with other published reports.²⁻⁹ During the ensuing five years the children were tested at intervals and were given varying amounts of alum-precipitated tetanus toxoid subcutaneously or intradermally.

Persistence of Antitoxin After Primary Immunization.—Thirty-three children (Table II) were tested for serum antitoxin one year after the primary immunization. At that time the antitoxin level was 0.01 unit in three individuals, 0.1 unit or more per cubic centimeter in twenty, and ten of the group had more than 0.25 unit per cubic centimeter. After thirty months the sera of another group of twenty-nine individuals were titrated. Sixteen of these had 0.01 unit per cubic centimeter, ten had 0.1 unit, and only three 0.25 unit of antitoxin per cubic centimeter. The third group of fifteen individuals, tested five years after the original two doses of toxoid, showed a lower titer of antitoxin. One individual had less than 0.01 unit per cubic centimeter,

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*No serum antitoxin titrations were done before the primary immunization since tetanus antitoxin is not found in appreciable amounts in the serum of nonimmunized individuals. The protective level of 0.1 c.c. was taken, though this probably is a higher level than is necessary for complete protection. Sneath² found that individuals given a prophylactic dose of 1,500 units of tetanus antitoxin had maximum of 0.1 to 0.25 unit per cubic centimeter of blood serum after one week.

TABLE I. UNITS OF TETANUS ANTITOXIN PRODUCED IN BLOOD SERA BY ALUM-PRECIPTATED TETANUS TOXOID

UNIT	NO. OF CHILDREN	PER CENT
<i>Forty-five days after injection of 1 c.c. toxoid</i>		
Less than 0.01	2	2.2
0.01	75	81.5
0.1*	13	14.1
0.25	2	2.2
Total	92	
<i>Fifty-four days after second injection of 1 c.c. and 127 days after first</i>		
0.1*	5	5.8
0.25	18	21.2
0.5	26	30.6
1	31	36.5
2	3	3.5
3-5	2	2.4
Total	85	

*Protective level.

TABLE II. PERSISTENCE OF SERUM ANTITOXIN IN CHILDREN WHO RECEIVED TWO DOSES ONE CUBIC CENTIMETER ALUM-PRECIPTATED TETANUS TOXOID WITH AN INTERVAL OF SEVENTY-THREE DAYS

UNITS OF ANTITOXIN PER C.C. OF SERUM	TIME AFTER THE LAST INJECTION OF TETANUS TOXOID			
	54 DAYS	12 MONTHS	30 MONTHS	60 MONTHS
3-5	2			
2	3			
1	31			
0.5	26	3		
0.25	18	7	3	
0.1	5	20	10	2
0.01		3	16	12
Less than 0.01				1
Total Number of Children	85	33	29	15

twelve had 0.01, and only two had 0.1 unit of antitoxin per cubic centimeter. Thus there was a gradual decrease in titer so that the majority of individuals were below 0.1 unit in thirty months, and thirteen of fifteen were below this level at sixty months.

The Effect of a Stimulating Dose of 1 c.c. at the End of One Year.—Thirty-five children were given 1 c.c. of alum-precipitated toxoid one year after completion of the basic immunization. The response (Table III) was rapid and marked. Before stimulation, twenty-three of thirty-three children had 0.1 unit or less per cubic centimeter, and no child had more than 0.5 unit per cubic centimeter. One week after stimulation, all had 2 units or more per

TABLE III. EFFECT OF STIMULATING DOSE OF 1 C.C. ALUM-PRECIPTATED TETANUS TOXOID AFTER ONE YEAR
TITRATIONS DONE ONE WEEK AFTER STIMULATING DOSE

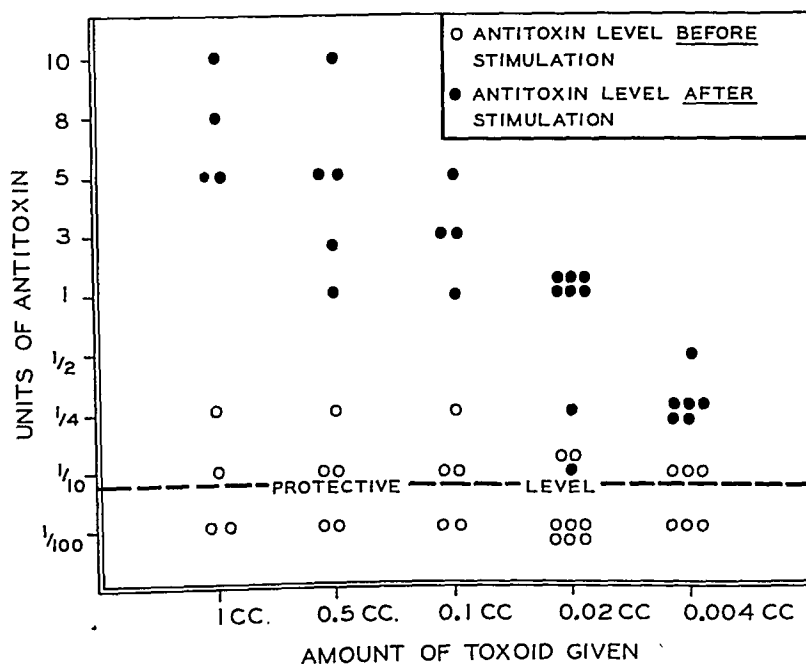
BEFORE STIMULATION		AFTER STIMULATION	
UNITS OF ANTITOXIN PER C.C. OF SERUM	NO. OF CHILDREN	UNITS OF ANTITOXIN PER C.C. OF SERUM	NO. OF CHILDREN
0.01+	3	2	2
0.1+	20	4	8
0.25+	7	6	14
0.5+	3	10	9
		15	2

cubic centimeter, and twenty-five of thirty-five children had 6 or more units per cubic centimeter. Titrations were again done on nine of this group eighteen months after the stimulating dose when the serum levels varied from 0.1 to 1 unit of antitoxin per cubic centimeter.

The Effect of Stimulating Doses After Two and One-half Years.—Chart I shows the stimulating effect of varying amounts of tetanus toxoid injected subcutaneously thirty months after the basic immunization. Four individuals who had from 0.01 to 0.25 unit of antitoxin per cubic centimeter when given 1 c.c. of toxoid responded in one week with a level of 5-10 units of antitoxin per cubic centimeter. When 0.5 c.c. of toxoid was given to five individuals with similar levels, the rise was to 1-10 units per cubic centimeter with a greater spread in the response. When 0.1 c.c. was given to five individuals, the rise was to 1-5 units per cubic centimeter. Eight individuals were given 0.02 c.c. of toxoid with a rise from 0.01-0.1 to 0.1-1 unit per cubic centimeter. When 0.004 was given to six individuals, the rise was from 0.01-0.1 to 0.25-0.5 unit per cubic centimeter. It is evident that while adequate levels may be reached with 0.004 c.c. of toxoid, 0.1 c.c. is probably the smallest practical "booster" dose. Thus the usual stimulating dose of 1 c.c. (often using a toxoid which is twice as potent) would seem to be entirely unnecessary as well as more dangerous so far as reactions are concerned.

CHART I

RESPONSE TO INJECTION OF VARYING AMOUNTS OF ALUM
PRECIPITATED TETANUS TOXOID 30 MONTHS
AFTER THE PRIMARY IMMUNIZATION

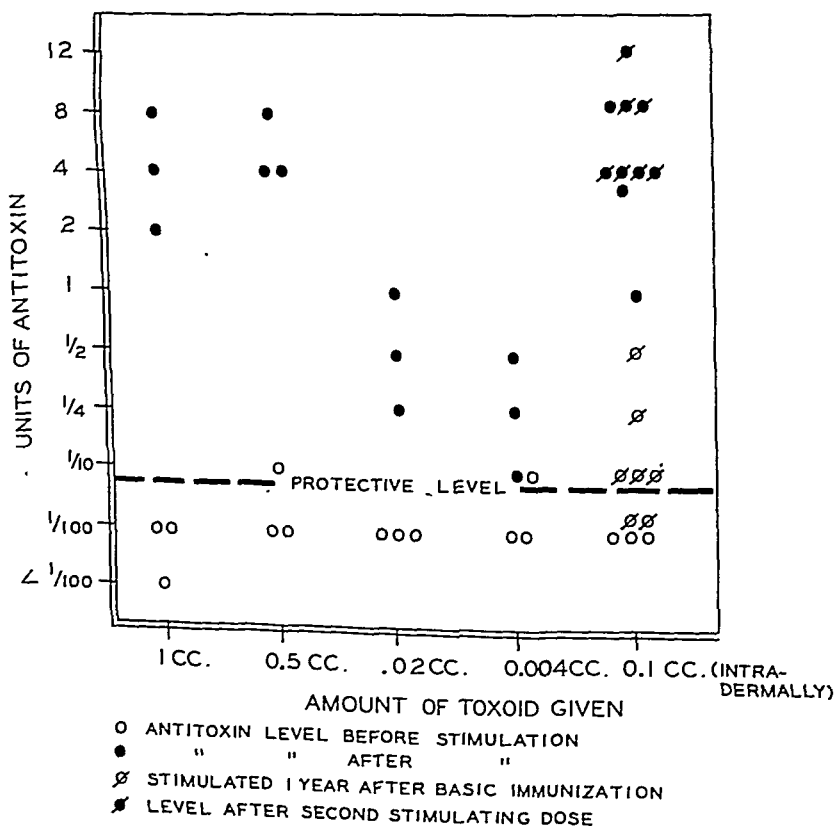


The Effect of Subcutaneous and Intradermal Stimulating Doses After Five Years.—Chart II shows the effect of subcutaneous and intradermal injections of tetanus toxoid in varying amounts five years after the basic immunization. One individual with less than 0.01 unit of antitoxin per cubic centimeter, and two with 0.01 per cubic centimeter were given 1 c.c. of alum-precipitated toxoid subcutaneously. The rise was to 2-8 units antitoxin per cubic centimeter. Three individuals with 0.01-0.1 unit per cubic centimeter were given 0.5 c.c. of toxoid resulting in a rise to 4-8 units per cubic centimeter, while three with 0.01 unit per cubic centimeter showed a rise to 0.25-1 unit per cubic centimeter when stimulated with 0.02 c.c. of toxoid. Administration of .004 c.c. of toxoid resulted in a smaller rise to 0.1-0.5 unit per cubic centimeter.

The effect of intradermal administration of 0.1 c.c. of alum-precipitated tetanus toxoid after five years (Chart II, Column 5) was determined in 10 individuals. Sera of five children who had been given a stimulating dose of 1 c.c. of alum-precipitated toxoid one year after the basic immunization had

CHART II

RESPONSE TO INJECTION OF VARYING AMOUNTS OF ALUM
PRECIPITATED TETANUS TOXOID 5 YEARS AFTER
THE PRIMARY IMMUNIZATION



levels varying from 0.01 to 0.5 unit per cubic centimeter. One week after they received 0.1 c.c. toxoid intradermally the level was 4-12 units antitoxin per cubic centimeter. Three individuals who had not been stimulated had 0.01 unit per cubic centimeter and had rises to 1, 4, and 8 units per cubic centimeter. Thus it would seem from these figures that 0.1 c.c. toxoid intradermally is perhaps as valuable as 0.5 c.c. subcutaneously.

DISCUSSION

The marked increase in serum antitoxin content resulting from the injection of 0.004 c.c. of toxoid subcutaneously five years after the original immunization would lead one to believe that the stimulating dose may be unnecessary, although caution dictates its use. When the basic immunity has been well established, the presence of actual infection should cause the immunized individual to respond with rapid antitoxin formation. The response in our series was rapid and adequate, regardless of the level to which the antitoxin had fallen in the periods since primary immunization.

This series was done entirely on Negro children. It has been stated occasionally that the Negro reacts with greater antitoxin formation than does the white child. If this is true it may explain the higher antitoxin levels obtained by us than by other workers. The ages at the time of the primary immunization varied from 3 to 8 years. The children were almost equally divided as to sex. No difference in antitoxin response was noted for either age or sex.

The interval of two and one-half months between the primary doses resulted in an adequate response. Bigler and Werner⁸ report that the optimum interval between injections is three months.

Reactions were not severe in any of the individuals. All of those of school age were able to continue in school. About 10 per cent of the children complained of soreness at the site of injection. Twenty-four hours following the intracutaneous injection of 0.1 c.c. of alum-precipitated toxoid an area of erythema varying from 2 to 6 cm. was noted. A small nodule was formed which disappeared in about four weeks. No abscess formation or necrosis occurred. One would expect more severe skin reactions in white children so that plain tetanus toxoid probably would be better as a routine intradermal stimulating substance.

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ESTABLISHMENT OF A TRANSFUSION CLINIC

TREATMENT OF MEDITERRANEAN ANEMIA IN THE OUTPATIENT DEPARTMENT

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THE successful management of severe Mediterranean (Cooley's) anemia requires frequent blood transfusions. It is only since the introduction of this therapeutic agent that a few children with this illness have survived to and beyond adolescence. Atkinson¹ reported two cases, siblings, 17 and 20 years old, who were followed from early childhood. They had typical bone and blood findings of Cooley's anemia. One child did not require transfusions and the hemoglobin level remained approximately 8 Gm. per 100 c.c. of blood. Aside from a late menarche she was apparently normal. The other sibling, a boy, had a more severe anemia which appeared to be benefited by splenectomy. He required one subsequent hospital admission and remained well thereafter. Smith² describes a patient who was then 23 years old. He had characteristic findings of Cooley's anemia. Prior to 1929 he had required five admissions to the hospital, but since that time his hemoglobin had been maintained at approximately 8 Gm. per 100 c.c. of blood. The disease in these patients was not comparable in severity with the cases to be described. Irrespective of the apparent severity of the disease there is always the possibility of spontaneous remissions, an outcome which has been observed in a few cases followed at the New York Hospital. It is, therefore, essential that all efforts be made to keep alive patients with this illness.

SUBJECTS

Six children with the severe form of Cooley's anemia have been followed at the New York Hospital for several years. They vary in age from 2 to 10 years. Prior to the establishment of the transfusion clinic these children required frequent hospitalizations for transfusion and other illnesses which often accompanied the anemia. These illnesses usually involved the upper or lower respiratory tract, but cardiac complications were not uncommon. Reference to Table I reveals the frequent number of hospitalizations required by the children: 7 for the youngest child, and 45 for the oldest child. The total number of patient-days in the hospital was 1,774; the total number of transfusions was 651, consisting of 101,800 c.c. of blood. It may be noted that hospital admissions were becoming more frequent as the patients grew older. Any normal continuity of home and school life was impossible.

In March, 1944 (seventeen months before time of writing), a transfusion clinic was established to treat these patients on an ambulatory basis. Initially, only two children were accepted for the clinic. However in November, 1944

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TABLE I. HOSPITAL ADMISSIONS, TRANSFUSIONS, AND ILLNESSES PRIOR TO ESTABLISHMENT OF THE TRANSFUSION CLINIC

CASE	AGE (YR.)	ADMIS- SIONS	DAYS IN HOS- PITAL	ADMISSIONS IN YEAR PRIOR TO CLINIC TREAT- MENT	TRANS- FUSIONS	C.C. OF BLOOD	SEVERE ILLNESSES
1	8	12	143	5	64	10,300	8
2	6	11	170	4	70	11,500	10
3	6	18	220	8	111	19,500	5
4	7	27	509	5	145	22,000	6
5	2	7	75	6	37	4,500	2
6	10	45	657	5	224	34,000	19
Total		120	1,774	33	651	101,800	50

TABLE II. SUMMARY OF OUTPATIENT DEPARTMENT THERAPY

CASE	MONTHS IN O.P.D.	TRANSFUSIONS	C.C. OF BLOOD
1	16½	52	18,350
2	16½	48	16,400
3	8½	23	8,700
4	8½	21	8,250
5	5	16	3,100
6	5	14	4,900
Total		174	59,800

(eight months before time of writing), two other children were added to the group. In February, 1945 (six months before time of writing), the group of six was completed. Table II shows the number of transfusions and amount of blood utilized since the establishment of the clinic. Fig. 1 is the graphic representation of hemoglobin levels in Case 1. The first part of the chart reveals the large irregular changes in hemoglobin value with the levels falling to 5 or 6 Gm. and then being restored by hospital transfusion. The second portion of

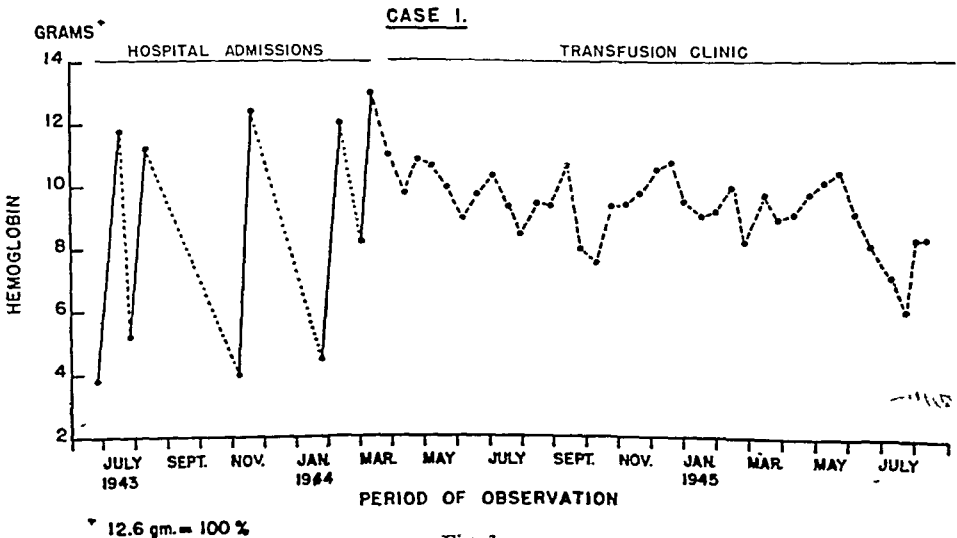


Fig. 1.

the graph represents a year and a half of experience in the transfusion clinic with the hemoglobin values stabilized around 9 Gm. Except for minor respiratory illnesses the entire group has been well, required no hospitalization, and has been regular in school attendance.

METHODS AND MATERIALS

The equipment consists of a transfusion set, sterile gauze, medicine glass, tourniquet, and adhesive tape. The transfusion set is equipped with a three-way stopcock at the junction of syringe and needle, so blood can be either pumped in or allowed to flow by gravity. Type O red blood cells obtained from the Red Cross Blood Donor Center are used exclusively. For the first six months the red cells were suspended in saline and subsequently in 10 per cent corn syrup.

The patients arrive at noon when blood is drawn for counts and cross-matching. The blood studies consist of hemoglobin determination, red blood cell count, and volume of packed red cells; occasionally a white count and differential are done. When the clinic was first established, 250 c.c. of blood were given each child every week. It is possible to prolong the interval to every two weeks if from 450 to 500 c.c. of blood are used. This is now the routine except in the case of a 2-year-old boy who receives 250 c.c. every two weeks. Approximately one hour is allowed for each transfusion to be completed.

Following the transfusion the children are permitted to play quietly. If reactions occur, they take place within one hour following transfusion. Therefore, temperatures are taken one hour after treatment and if they are not elevated above 39° C. (103° F.) and there is no severe reaction, the patients may leave. It has been unnecessary to keep any patient longer than two hours after transfusion.

TRANSFUSION REACTIONS

Transfusion reactions have been of frequent occurrence and have been completely unpredictable and inexplicable. They may be grouped as follows:

a. Fever, chills, and headache, usually mild and transient, are often relieved by acetylsalicylic acid.

b. Asthma and urticaria occurred twice each and responded to adrenalin.

c. Hemolysis—one severe hemolytic reaction accompanied by deep jaundice and nausea was treated by bed rest and diet. A few milder attacks have occurred.

d. Local pain along the course of the vein occurs in a few patients if the blood is injected rapidly.

None of the reactions have been severe enough to require hospitalization or discontinuation of outpatient department therapy.

CASE HISTORIES

CASE 1.—R. P. was a 7-year-old girl of Italian ancestry whose anemia was first detected in 1939. The anemia is associated with hepatosplenomegaly and typical x-ray and blood findings of Cooley's anemia. From 1939, to March, 1944, she was hospitalized twelve times;

five of these admissions occurred in the year prior to establishment of this clinic. She spent 143 days in the hospital and received sixty-four transfusions consisting of 10,000 c.c. of blood.

On March 10, 1944, transfusions in the clinic were started. At this time the patient's hemoglobin was 13 Gm. per 100 c.c. of blood, red cell count was 3.8 million per 100 c.c., and volume of packed red cells was 30. She has been transfused every one or two weeks since then and has had a total of fifty-two transfusions consisting of 18,350 c.c. of suspended red cells. The hemoglobin at the time of writing was 8.4 Gm.; red cell count, 3.9 million; and volume of packed red cells, 29. She experienced occasional febrile responses, slight headache, and chills following transfusions. Her health has been good except for a few mild respiratory infections.

CASE 2.—J. P. (brother of R. P.) was a 6-year-old boy who was first seen at the New York Hospital when 4 months old. Hepatosplenomegaly was found and blood count revealed a hemoglobin value of 8 Gm. per 100 c.c. Blood smear showed stipple, target and nucleated red blood cells. The first hospital admission was in February, 1939, because of weakness and a severe upper respiratory infection. He has had ten subsequent admissions, four of which were in the year previous to the establishment of the transfusion clinic. Severe respiratory infections have always accompanied this boy's anemia, and on the last nine admissions he required sulfonamide therapy. He was hospitalized for a total of 170 days and received 11,000 c.c. of blood in seventy transfusions.

Outpatient department transfusions were started March 17, 1944. The blood count was hemoglobin 11.8 Gm. per 100 c.c. of blood; red cell count, 3.7 million per 100 c.c.; and volume of packed red cells was 34. He has since been transfused forty-eight times, and received 16,400 c.c. of suspended red cells. The hemoglobin has varied from 8 to 12 Gm. per 100 c.c. of blood. The last determinations showed hemoglobin, 8.6 Gm.; red blood cell count, 3.3 million; and volume of packed red cells, 29. Following transfusions he has had some febrile reactions; on two occasions he had urticaria; and he had one severe asthmatic attack. His health, since March, 1944, has been good except for mild respiratory infections.

CASE 3.—S. S. was a 7-year-old girl of Greek extraction. Anemia was first noted at 10 months of age, but she did not require hospitalization until 3 years of age. At that time the hemoglobin was 8.5 Gm. per 100 c.c., and blood smear and bone changes were typical of Cooley's anemia. She had an enlarged liver and spleen. This first admission was associated with a peritonsillar abscess. Since then she has had seventeen admissions, most of which have been uncomplicated. She received 19,500 c.c. of blood in 116 transfusions.

This patient's first outpatient department transfusion was on Nov. 10, 1944. At this time the hemoglobin was 10 Gm. per 100 c.c., red cell count was 3.6 million, and volume of packed red cells was 26. In the past eight months she has received twenty-three transfusions totaling 8,700 c.c. of blood. She has had occasional febrile reactions and chills. The last hemoglobin determination was 8.8 Gm.; red cell count, 2.8 million; and volume of packed red cells, 31. During the year before clinic transfusions were begun the patient was hospitalized eight times. In the eight months since the patient joined the group her health has been good.

CASE 4.—J. F. was a 7-year-old boy of Italian parentage. He was first seen at the New York Hospital at age of 3 months because of bronchopneumonia and otitis media. The next admission was one month later because of pneumonia. He was extremely ill and was discovered to have Cooley's anemia. A splenectomy was performed when he was one year old. Since then he has remained fairly well except for the recurring anemia. He has had twenty-seven admissions to the hospital totaling 509 days and has received 22,000 c.c. of blood in 145 transfusions.

This patient started attending the transfusion clinic Nov. 10, 1944, at which time the hemoglobin was 10 Gm. per 100 c.c. of blood, red cell count was 3.3 million, and volume of packed red cells was 30. Following the first transfusion he had fever and a slight chill; the following day he became markedly jaundiced. He remained deeply icteric for two weeks but did not require hospitalization. Subsequent transfusions have been uneventful. He has received twenty-one transfusions consisting of 8,250 c.c. of red cells. The last hemoglobin

determination was 8.6 Gm., red cell count was 3.2 million, and volume of packed cells was 31. The year before attending this clinic the patient required hospitalization five times; this year he has been in excellent health.

CASE 5.—D. B., a 2-year-old Italian boy, was admitted to the New York Hospital because of pallor and hepatosplenomegaly, when 4 months old. Blood findings were consistent with the diagnosis of Cooley's anemia, but x-rays of skull and long bones were normal and have remained so. He has had six subsequent hospitalizations during which time he received seventy-five transfusions of 4,500 c.c. He was added to the outpatient group Feb. 2, 1945. Since then he has had sixteen transfusions consisting of 3,100 c.c. of blood. He has had no reactions to transfusions but has presented the mechanical problem of finding suitable veins. The blood on last determination showed hemoglobin, 9.4 Gm. per 100 c.c.; red cell count, 3.2 million; and volume of packed red cells, 28.

CASE 6.—I. C. was 10 years old. Her parents were Sicilians. She had a twin brother who had the trait but not the active form of Cooley's anemia. Pallor was noted at birth, and a diagnosis of Cooley's anemia was established when she was 17 months old. She also has a complete situs inversus. She has had forty-five hospital admissions; five of these were in the year prior to start of clinic therapy. During the early years she required hospitalization approximately every seven weeks. She had a splenectomy when 3 years old and has required transfusions about every eleven weeks since. She has had many severe respiratory infections associated with the anemia and has also had one attack of pericarditis with effusion. When she becomes anemic she develops severe headaches and chest pain. She has spent 657 days in our hospital and received 34,000 c.c. of blood.

The patient started clinic transfusions on Feb. 23, 1945. At this time the hemoglobin was 9.8 Gm. per 100 c.c., red cell count was 3.9 million, and volume of packed red cells was 32. She has had fourteen transfusions consisting of 4,900 c.c. of blood. The last hemoglobin determination was 9.2 Gm.; red cell count, 2.9 million; and volume of packed cells was 30. She has always had severe headaches and chills following transfusions; these have not been so severe in the outpatient department.

COMMENTS

Treatment of our patients with Cooley's anemia in the outpatient department was undertaken for several reasons:

1. Repeated hospitalizations interfere with the normal continuity of home and school life.
2. Sustenance of adequate blood levels is physiologically more sound than replenishment of blood at irregular intervals.
3. Reduction in hospital expense.
4. Better utilization of available bed space in a teaching institution.

With the establishment by the American Red Cross of centers for collecting blood plasma, residual red blood cells have been obtainable in abundance. These cells are reportedly equal in therapeutic efficacy to whole blood³ in treating severe anemias, and their use eliminates the necessity for obtaining blood donors. It is only because of the ready availability of these cells that the outpatient department transfusion clinic has been feasible. The American Red Cross, with the end of World War II, has temporarily abandoned its project of blood collection.* This is unfortunate, as the red cells can be used to treat many

*Since August, 1945, we have had seven months' experience using only whole bank blood and we find this more satisfactory in maintaining good blood levels.

forms of anemia which must once more be treated with whole blood. It is hoped that the blood bank will be re-established as a permanent peace-time institution.

SUMMARY

1. The establishment of an outpatient transfusion clinic is described.
2. Type O washed red blood cells obtained from the Red Cross Blood Donor Center are used exclusively. These are supplied free and are essential to the maintenance of the clinic. It is to be hoped that these cells will be available in the postwar period.
3. The case histories of six patients with severe Mediterranean anemia are presented. These patients formerly had many serious illnesses and required frequent hospitalizations. Since attending the transfusion clinic they have been in good health, and the five older children have attended school regularly for the first time. The first two patients admitted to the clinic have now been followed for seventeen months.
4. An outpatient clinic of the type described can probably be organized to treat any form of chronic anemia requiring repeated interval transfusions.

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DOES MILK BETWEEN MEALS HAMPER THE APPETITE OR FOOD INTAKE OF THE CHILD?

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THE studies here described owe their motivation to a thesis laid down before the American Pediatric Society in 1940, by one of its senior members, to the effect that: "Milk requires 3 to 3½ hours for complete gastric digestion. . . To give it at 10:30 [in school] and then send the child home for lunch at 12 violates the rules of physiology, dietetics and common sense. Experience shows that the appetite for lunch may be much impaired." That "routine feeding of milk midway between meals is certainly not advisable," was concurred in by two discussors, whereas only one dissent was mildly voiced: "There are great individual differences in the ability of children to take it and get along well on it."¹

Is it truly unwise to offer children, as is so often done in schools and homes, a glass of milk in mid-morning or mid-afternoon? In studies by the writer on the physiology of milk digestion during childhood,² no appetite-impairing effect from milk had been noted. The same studies had indicated that following the drinking of 8 ounces of milk the gastric emptying time may range from 50 to 170 minutes; the mean of 122 experiments was almost exactly 120 minutes.

It seemed worth while, therefore, to determine more directly whether milk impairs the appetite. A controlled series of feeding experiments could be expected to yield more reliable information than would be gained by sporadic interviews of random patients and their mothers—which kind of data, partially subjective, appeared to have served as the bases for the opinions just cited.

Available for testing purposes was the same large group of children, recuperating from rheumatic fever in a rest home but otherwise well. All had been through one or more episodes of acute illness in the preceding year or two, necessitating complete bed rest for weeks or months, but were now in the recovery phase, free from fever and active symptoms, and ambulant for the greater part of the day. Institutional residency had taught them how to co-operate with nurses and doctors without growing resistant or emotional.

The research program, as finally planned and carried out, was composed of two separate sets of experiments. The first, a long-range clinical survey, consisted of giving each day to the 59 children in the rest home a supplementary glass of milk one hour before noon dinner and again one hour before supper. This feeding program was continued for nearly five months. Pasteurized milk and homogenized milk were alternately fed, with observation of the children for symptoms attributable to the added milk before meals.*

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*Pasteurization is an integral part of the homogenizing process. Unless heat treatment accompanies the homogenizing to the extent necessary for killing of bacteria, the lipase present will become activated, and the milk grows rancid in a few minutes. In this paper the term "pasteurized" refers to plain or whole milk; the term "homogenized" refers to milk which has been both pasteurized and homogenized.

The second part of the program consisted of a shorter but much more detailed dietary balance study. For successive single weeks the spontaneous food intakes of 18 children were measured carefully, in a quantitative comparison of the amounts of food taken: (a) when glasses of pasteurized or (b) homogenized milk were given before each of the three meals, with (c) when the milk before meals was omitted.

Testing two types of milk in this feeding study made it feasible to explore a related but subsidiary problem. From the standpoint of hampering the appetite or food intake, does a hard-curd milk such as pasteurized milk have effects different from those of a soft-curd milk such as homogenized milk? If curd size and texture are the factors responsible, homogenized milk with its smaller softer curds should produce less impairment of appetite than does pasteurized milk. Homogenized milk is the soft-curd milk most widely sold. Pasteurized milk was responsible for the criticisms quoted in the first paragraph of this paper.

In institutions for treatment of children with rheumatic fever it is a common observation that these patients are subject to occasional episodes of nausea and vomiting which come on spontaneously without obvious cause. Though most frequent in the morning, before breakfast, they may occur at any hour of the day or night. For the purposes of the present question this propensity to gastrointestinal irritability was not unwelcome. It might help to evoke or accentuate whatever disturbances are elicitable by milk.

In the first experiment, which was essentially a screening test, it was hoped that by feeding milk before meals to a large number of children over an appreciable length of time a small group of more sensitive children would be discovered who would manifest the expected symptoms of anorexia or gastrointestinal distress more or less regularly. From observation of such children it would be possible to determine whether there were any differences in their reactions to the two forms of milk.

For this experiment all the children in the rest home were used. There were 59 altogether, ranging in age from 3 to 14 years; 28 boys and 31 girls. All were white. Since the girls were housed on the first floor and the boys on the second, each floor having its own serving kitchen, it was expedient to treat the boys as one experimental subgroup, and the girls as the other. Supplements of milk were served to each child twice daily. One 7 ounce glass was given at 11:00 A.M., an hour before dinner, and a second glass at 5:00 P.M., an hour before supper. While homogenized milk was being served on one floor, pasteurized milk was being served on the other. Regularly each month the two types of milk were alternated to avoid the possible influence of a sex difference. These supplementary glasses of milk were given between February 15 and June 30, a continuous period of 19 weeks.

Because the milk, market grade, was purchased in turn from five different Philadelphia dairies, the source each month was a different region of the local milk shed. The changing from one dairy to another was placed midway between the changing of the children from pasteurized to homogenized milk and vice versa. At all times the pasteurized and the homogenized milk came from the

same receiving vats, so that all differences existent between the two were secondary only to the process of homogenizing. In cream content the range was from 3.8 to 4.2 per cent, with a mean approximating 4 per cent. Over the months the curd tension of the pasteurized milk fluctuated between 24 and 43 Gm., with a mean of 33.6 Gm. The homogenized milk had a much lower range—5 to 17 Gm., with a mean of 10.7 Gm.

The children drank the extra milk without urging or coaxing and seemed to enjoy it. Refusals were extremely infrequent. At times a child would request and be given two glasses instead of the customary single serving. Multiplying the number of these feedings of milk before meals by the number of children, yields the round figure of 16,000—representing the approximate number of times that opportunity was afforded for the hypothesized deleterious effect of milk to manifest itself.

No diminution in appetite became evident for any of the 59 children over the period of the study as compared with the weeks immediately preceding or following, neither with the pasteurized nor with the homogenized milk. The requests for second portions were as abundant as ever and coaxing to eat did not become necessary. In fact, during the nineteen weeks the experiment lasted, none of the children were afflicted with an episode of intra-abdominal distress with vomiting, pain, or diarrhea.

In short, on crude observation, no unwelcome symptoms were displayed by any member of this large group of institutionalized children which could be attributed wholly or in part to receiving a glass of milk an hour ahead of a principal meal.

The more quantitative study was accordingly instituted, to ascertain by direct measurement whether taking of milk before meals would cut down the total daily intake of other foods. Accurate records were kept of the amounts and composition of all articles of food taken by each of 18 children given an unlimited diet: (a) during a week when a glass of pasteurized milk was taken three times daily, one hour before each meal; (b) during a week when homogenized milk replaced the pasteurized milk; and (c) during a one-week control period.

The 18 children, white, aged 5 through 11 years, were distributed in three groups, A, B, and C, each composed of three boys and three girls. The average age of the members of group A was 7.3 years; of group B, 7.8 years; of group C, 7.5 years. As judged by Faber's² standards for weight as related to height and age, five of the children were overweight, eleven were in normal range, and two were underweight.

The feeding of milk before meals to these groups was staggered, in order to equalize the influence of climatic and other environmental conditions upon appetite and energy requirements:

	Group: A	B	C
1st week	Pasteurized Milk	Homogenized Milk	None
2nd week	Homogenized Milk	None	Pasteurized Milk
3rd week	None	Pasteurized Milk	Homogenized Milk

Save for the added milk, the diets given the three groups were identical in day-to-day composition, and all items were offered in unlimited quantities.

The daily menus were planned independently of this experiment. Their pattern was in accord with common practices of child feeding as determined by the foods available locally. A typical schedule consisted of: Breakfast: dry cereal with milk and sugar, bread and butter, milk; Dinner: meat, a white vegetable, two green vegetables, bread and butter, dessert, milk; Supper: cereal or sandwiches, milk, fresh or stewed fruit. Such a diet meets the nutritional needs of growing children fairly well; its most serious defect was the relatively low content of fresh citrus fruits. Since menus of this type had been in constant use in the institution for a long time, corrective changes were not initiated prior to the feeding experiment in order not to confuse the kitchen personnel. It was thought furthermore that any beneficial effects contributed by the added milk might be demonstrated more prominently if the basic diet were not ideal.

Individual over-large portions of everything were served to the children. As the loaded food trays were prepared in the kitchen the quantities of every item on each plate were weighed or measured accurately; when they were returned to the kitchen similar measurements were taken of the quantities left uneaten. With each meal separate pitchers of pasteurized milk were set out from which each child helped himself to as many glasses as he wanted. The differences between what was served and what was returned gave the amounts ingested. It was not feasible to measure the fluid balances of the children inasmuch as their drinking water was obtained from fountains of the jet type. Glasses of water were not placed on the mealtime trays.

The consumption of nutrients of each child for each week was then computed according to the analytic values compiled by Taylor.⁴ Protein, fat, carbohydrate, calcium, phosphorus, iron, vitamin A, thiamine, ascorbic acid, riboflavin, acid-base ratio, and total calories were measured. Totals were prepared to describe the complete intake of all nutrients (a) inclusive of, and (b) exclusive of, the 21 ounces of milk before meals.

Review of the data impressed one with the wide divergences in weekly intakes of the many factors measured. These differences in the amounts taken by the various children bore no obvious correlations with sex or age. Such differences were not unexpected, since, as Macy⁵ and others have emphasized, it is common for normal children to exhibit short-term wide fluctuations in external metabolic equilibriums. In general, however, more of every nutrient was taken in the two weeks when the milk supplements were given than in the control week which was supplement-free. As an example, the findings for weekly calorie intakes are presented (Fig. 1). The increases ranged from 1 to 52 per cent over the controls, except with one boy of 8 years in the week he received pasteurized milk.

The individual children showed marked differences in calories consumed in the respective weeks supplemented with the two forms of milk. Yet, as demonstrated by the almost perfect identity of the mean values for calories, these dissimilarities were without specific regularity. Taking the control week as the 100 per cent base line, there was an 18.8 per cent rise for the week with pas-

teurized milk supplement and a 19.6 per cent rise for the week with homogenized milk supplement.

With biologic data exhibiting marked fluctuations, conclusions are not of significance unless drawn from central tendencies exhibited by the group as a whole. Therefore, for each nutrient, the intake of each child in each separate week was converted to percentages with the control week as 100 per cent, and the mean percentages for the respective experimental weeks computed from these individual percentages. The reason for converting to a percentage basis before proceeding with the calculations rested upon the necessity for each child's intake to have equal weight in the final scoring. Otherwise the greater quantities consumed by some children would overshadow unfairly the smaller amounts taken by others. For ready presentation the final comparisons have been arranged in diagrammatic form (Fig. 2).

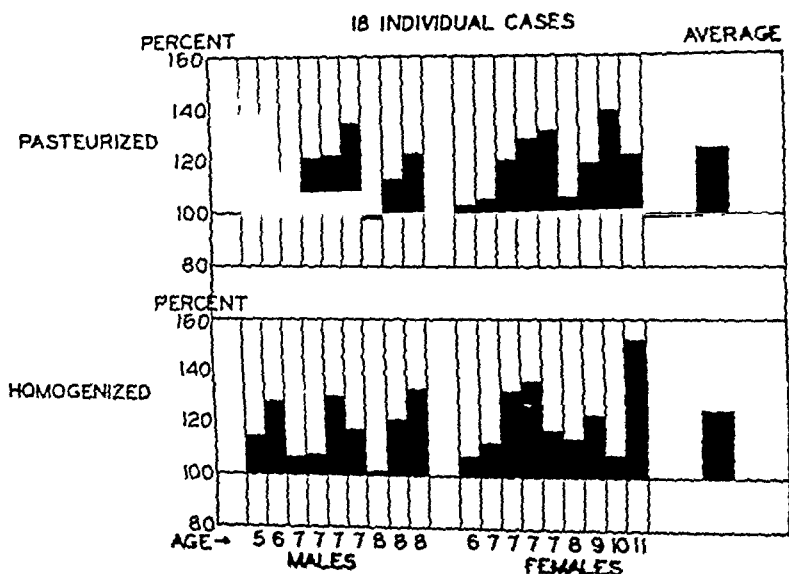


Fig 1--Diagram illustrating the weekly caloric intakes of the eighteen children when receiving 21 ounces of supplemental milk per day, 7 ounces before each meal. The base line of 100 per cent is the intake during the control week when extra milk was not given. The upper half of the diagram represents the week with pasteurized milk. Each vertical block represents one child. With one exception all subjects consumed more calories when taking the supplementary milk than in the control week.

By statistical methods, using the *t* test of significance, the mean values for the weeks with the pasteurized and with the homogenized milk were found not to differ significantly one from another, except with respect to vitamin A. In other words, save for this one vitamin which was augmented only in the week with pasteurized milk, all intake differences between these two weeks were so small as to lie well within the limits of random sampling. The intakes of thiamine, ascorbic acid, riboflavin, calories, protein, fat, calcium, and phosphorus were found to have been augmented markedly in the weeks when milk before meals were given, as compared with the control week which lacked the milk supplements. For only one nutrient, iron, were the intakes during the weeks with milk not increased above the control week.

Fig. 2 demonstrates another point. By deducting from the total intakes during the weeks when one or the other milk was being given the amounts of each nutrient supplied by the milk before meals, it appears that, apart from vitamin A, the amounts of the various nutrients taken *during* meals in each of the three weeks of testing were all about equal. This held true whether homogenized milk, pasteurized milk, or no milk at all had been taken before meals.

The convalescent hospital where these studies were made is efficiently run, with good care of the patients as its primary responsibility. It was of interest to evaluate the quality of the diet of this institution in terms of the nutritional

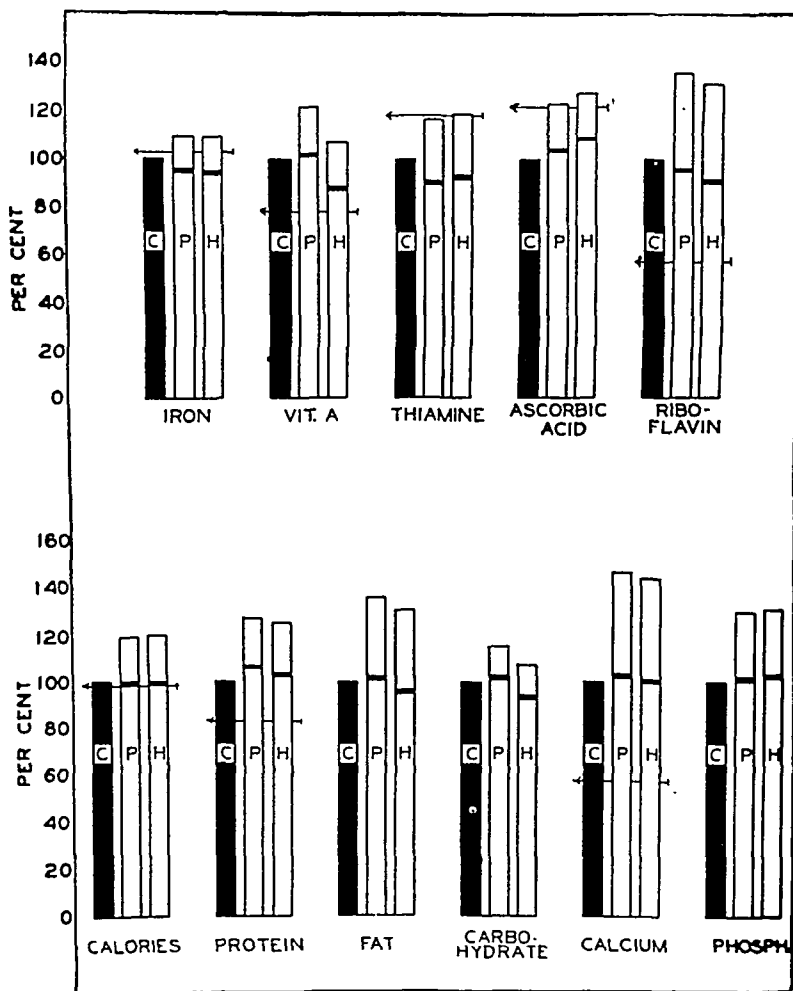


Fig. 2.—Diagram showing the comparative intakes of the nutrients measured. Each vertical block represents the pooled data from 18 children. All figures are relative, the values for the control week being set arbitrarily as 100 per cent. The first (C) unit in each group of three represents the control week with no before-meal milk. The second (P) and third (H) units represent, respectively, the weeks with pasteurized and homogenized milk before meals. The transverse bars in the P and H blocks mark off the fraction of total intake contained in the three glasses of milk (21 ounces) taken as supplements. The arrow symbols on the figures indicate the daily allowances for specific nutrients recommended by the Food and Nutrition Board of the National Research Council.³

standards currently proposed by the Committee on Foods and Nutrition of the National Research Council.⁶ (Fig. 2) If the amounts furnished by the 21 ounces of milk before meals were disregarded, the institutional diet, as taken to satiety by these eighteen children: (1) supplied protein, calcium, riboflavin, and vitamin A in more than liberal amounts, (2) just met the body needs for iron, (3) was deficient to a moderate degree in thiamine and ascorbic acid, and (4) conformed almost precisely with the proposed standards in caloric energy content. But if the amounts of nutrients in the supplementary 21 ounces of milk before meals were now added to the computations, all shortages became corrected and the consumption of all nutrients including calories became further augmented. Following this study the daily menu of the rest home was altered to include more citrus fruits, cereals, and grains.

The milk before meals did not hamper the appetites of the children for milk during meals. Their daily intakes of milk averaged as follows:

	Before meals	At each meal	Daily total
Control week:		14.9 oz.	44.7 oz.
Week with 3 pasteurized milk pre-feedings:	21 oz.	14.7 oz.	63.2 oz.
Week with 3 homogenized milk pre-feedings:	21 oz.	14.7 oz.	63.2 oz.

These figures mean that every child at each meal helped himself to about two glasses of milk, on the average, regardless of whether or not an extra glass had been taken one hour previously. Of this, approximately 6 ounces daily were taken with the breakfast cereal; the remainder was consumed as a beverage.

If we scrutinize the mean composition of the meals taken during any of the three experimental weeks, we find that the daily 44.2 to 44.7 ounces of milk consumed at those meals supplied (in round numbers) the important percentages of the total intake of nutrients listed in column A:

	A	B
Calcium	85	150
Riboflavin	80	140
Fat	65	
Thiamine	55	45
Phosphorus	50	
Calories	40	40
Protein	35	27.5
Ascorbic Acid	35	
Vitamin A	30	50
Iron	30	27.5
Carbohydrate	30	

Column B lists, for comparison, the proportions of the daily requirements for children, as postulated by the Committee on Foods and Nutrition of the National Research Council, which are met by this volume of milk. Data such as these help to explain why pediatricians have always emphasized the great worth of milk as a food for the child.

COMMENT

Neither of the two sets of experiments furnished any evidence that the taking of milk between meals interferes with the child's eating of his next regular meal. In fact, under the conditions described, milk given before meals proved highly acceptable and seemed to be utilized metabolically by the experimental subjects as a sort of dietary bonus.

These experiments were carried out with a small number of children under specialized conditions, and cannot be taken arbitrarily as the basis for generalizations embracing all children. It is conceivable that different responses to supplementary milk feedings might be observed with children younger, or older, or better nourished, or physically more active, than those in the present series. It is conceivable also that the children here studied, being habituated to institutional living, were more passively receptive to environmental suggestion than children in their own homes would be. They may have viewed the milk before meals as a medicament helpful toward recovery, and therefore to be taken willy-nilly. Life at home and school contains scores of external influences foreign to those of institutional life, and vice versa, all capable of conditioning the child's appetite favorably or otherwise.

It is conceivable, also, that the metabolic needs of convalescent rheumatic fever patients may be greater than nonrheumatic normal children. The average healthy youngster needs daily about 1,600 calories at 4 to 6 years of age, and 2,000 calories at 7 to 9 years of age.⁶ A glass of 7 or 8 ounces of milk represents 140 to 160 calories; when served with cookies or bread the caloric content will be 200 or more. If such a feeding is given to a healthy youngster in mid-morning or mid-afternoon, and if in addition his meals earlier that day have been comparatively large, at the next regular meal his appetite may very well be poor, for the reason that a goodly portion of the total daily caloric requirement has been already satisfied. Recovery from a chronic illness such as rheumatic fever may call more urgently for a dietary supplement. Yet it is doubtful that this group of rheumatic fever convalescents were in genuine need of supplemental nourishment. For months prior to the experiments they had been on a liberal diet, with extra food being given between meals. At the time of the test only two were underweight. Moreover, their routine of living was sedentary, with expenditure of energy in physical activities much lower than that of well children being reared at home.

One hypothesis for the recounted unfavorable experiences with milk before meals suggests itself. In extremely cold weather and under other special circumstances market milk sometimes develops a high content of casein and fat and grows markedly hard-curd. Such milk—of curd tension often over 50 Gm.—may give rise to tough rubbery clots inside the stomach. Occasionally a child may suffer from a temporary reflex loss of appetite as a result. In the present study the pasteurized milk had an average curd tension of 33.6 Gm.; the homogenized milk, 10.7 Gm. The pasteurized milk was thus never strongly hard-curd. Perhaps if the digestive capacity of any of the children had been as feeble as that of a young infant, some difficulty might have been experienced in their

digesting of the moderately sized and moderately firm curds from the pasteurized milk. Earlier direct observations² of these children, however, had shown every one to have responsive secretory activity normal for the age period. As for homogenized milk, if properly processed and bacteriologically safe, as was the homogenized milk used here, infants can digest it readily without any gastrointestinal distress.⁷

No statements were made by the physicians cited regarding the fat content of the milk presumed to give rise to the digestive disturbances. Guernsey and Jersey milk which contains 5 to 7 per cent fat (and abundant protein in proportion) may be expected to slow gastric emptying more than does milk of commercial grade, such as that in the present study, with fat content ranging between 3.8 and 4.2 per cent.

It must be remembered that the acid of the gastric juice fades out temporarily during fever.⁸ The intragastric milk clotting then becomes altered; the coagulation becomes affected by the pepsin enzyme which, when acting alone, tends to produce large calcium-rich curds. Facilitating this trend toward larger curds is the element of fever itself. As the environmental temperature rises above normal body temperature caseinous clots exhibit a marked tendency to shrink by syneresis and grow tough and rubbery. Thus can be explained the nausea and vomiting occasionally seen following the taking of pasteurized milk during febrile illnesses. This tendency, of course, is less marked with homogenized and other more soft-curd milks, which give rise to smaller, softer, and presumably more readily digested curds.

SUMMARY

For nearly five months, 59 convalescent children in a rheumatic fever rest home were given a 7 ounce glass of milk twice daily, one hour before meals, homogenized and pasteurized milk being served in alternate months. These before-meal feedings failed to elicit in any child any undesirable symptoms of anorexia, gastrointestinal distress, or decreased consumption of food attributable to either type of milk.

Eighteen of these children were later subjected to a more quantitative 3-week diet-intake study. Extra milk, pasteurized or homogenized, was given in 7 ounce quantities three times a day, one hour before each meal, for two of the three weeks, and the amounts of food taken spontaneously during mealtimes were carefully measured. It was found that the amounts taken at mealtimes of calories, minerals, protein, and all other nutrients were approximately equal, both in the control week and when milk, whether pasteurized or homogenized, was fed before meals. The added milk proved a true dietary supplement, well taken, and both forms appeared to be equally well metabolized.

No evidence was found in these experiments to warrant advising the discontinuance of drinking milk between meals. The data indicated, on the contrary, that it is wise to make available such extra servings whenever there is need for improving a child's nutritional status or food intake.

Acknowledgment is due Miss Kathleen Cornell for measurement and calculation of the dietary components, and Miss Frances Hoag for many helpful suggestions.

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DYE POISONING IN INFANCY

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RECENTLY two episodes of dye poisoning have occurred on the pediatric service of the Louisville General Hospital, one in the hospital nursery and the other one in the isolation ward.

On Feb. 28, 1945, at 3:00 p.m. it was called to the attention of the pediatric house officers that one of the premature babies had become cyanotic (Case 1). Physical examination failed to reveal a cause for this condition. Four hours later another premature infant (Case 2) in the same unit became cyanotic. The following morning, a third infant (Case 3) was found to have a bluish tint to the lips and skin. Since these were the only babies in this unit, a common etiological agent was suspected. That evening all the newborn babies (thirty-two) in the adjoining nursery showed transient cyanosis. A thorough search for the presence of gas, insecticide sprays, disinfectants, and other poisons was made, but we were unable to discover an agent which could have produced such an episode.

On March 3, one of the nurses stated that on the day the cyanosis appeared, she had helped stamp diapers used in the nursery. It was found that the diapers had been stamped on all corners and both sides before being laundered. The hospital administration had changed their system from a central supply to an individual ward supply, necessitating a stamp for each department. The stamping ink bottle was found and was clearly marked, "This ink contains Aniline Oil which must be removed by laundering before the marked article is stocked or worn."

CASE 1.—B. P., premature female, was born Jan. 23, 1945; her birth weight was 3 pounds and $\frac{1}{2}$ ounce. Aside from a positive smear for gonorrhea in the mother, the family and prenatal history was not remarkable. The infant received 0.125 Gm. of oral sulfathiazole prophylactically every eight hours for three days. On February 28, she weighed 4 pounds and 10 ounces, and was receiving 40 c.c. of breast milk every three hours. At 3 p.m. it was discovered by the nurse that the infant was cyanotic. Physical examination failed to disclose the cause. Continuous oxygen was started but in spite of this the condition remained the same. The following day a roentgenogram of the chest (Fig. 1) was made and blood was drawn for methemoglobin determination. The blood had a marked chocolate color and clotted immediately. Blood examination revealed a red blood cell count of 2,540,000 per cubic millimeter with a hemoglobin of 8.5 Gm. per 100 c.c. of blood, and a white blood cell count of 2,650 per cubic millimeter with lymphocytes 47 per cent, polymorphonuclear leukocytes 49 per cent, and monocytes 4 per cent.

On March 2, the infant was still cyanotic. A transfusion of 30 c.c. of citrated blood was given intravenously and penicillin was administered, 2,500 units every three hours intramuscularly. Oxygen was continued due to the persistent cyanosis. On March 5, the red blood cell count was 2,320,000 per cubic millimeter with a hemoglobin of 8.0 Gm. per 100 c.c. of blood, and the white blood cell count was 12,350 per cubic millimeter with lymphocytes

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CASE 3.—B. T., premature infant, was born Feb. 11, 1945, after an uncomplicated pregnancy. The birth weight was $4\frac{1}{2}$ pounds. The mother, who had had antisyphilitic treatment for an infection of long duration, was also a known chronic alcoholic. On March 1, 1945, the infant weighed 5 pounds and 4 ounces and was given 50 c.c. of breast milk every three hours. At 9 A.M., just fourteen hours after the development of cyanosis in the second child, the infant was found to be markedly cyanotic. Twenty c.c. of $2\frac{1}{2}$ per cent glucose in normal saline was given subcutaneously and oxygen was administered. A roentgenogram of the chest was made the following day (Fig. 3). Two thousand and five hundred units of penicillin were given intramuscularly every three hours. A transfusion of 40 c.c. of whole blood was given intravenously. On this date the carbon dioxide combining power was 37.2 volumes per cent.

On March 3, the cyanosis had practically cleared, but as we had just learned the possible etiology, a blood sample was drawn for spectroscopic examination. It was negative for methemoglobin. The following day a red blood cell count was 4,550,000 cells per cubic millimeter with a hemoglobin of 15 Gm. per 100 c.c. of blood, and a white blood cell count of 13,900 per cubic millimeter with lymphocytes 49 per cent, polymorphonuclear leukocytes 41 per cent, and monocytes 10 per cent.

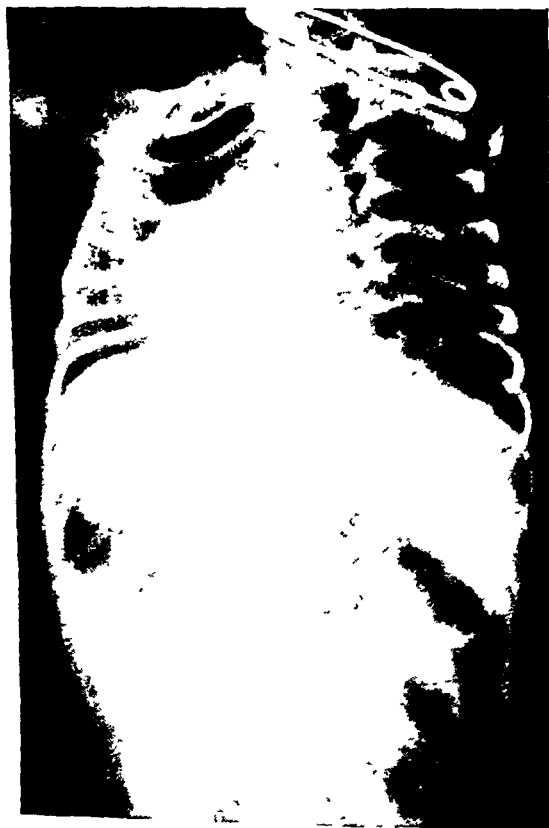


Fig. 2.—B. D. (Case 2). Roentgenogram taken March 1, 1945

On Sept. 15, 1945, three infants on the isolation ward became cyanotic. These were the smallest of eleven babies admitted to this ward because of nutritional disturbances. All three had severe diarrhea and excoriation of the buttocks. Careful check on all medications failed to reveal any drug which

was being administered to these children which was not also being received by the others. Because of the previous episode, search was made for newly stamped garments. The clothes of these three patients were stamped with aniline dye, but all had been laundered before use. Freshly stamped washcloths were found at the bedsides. The small cloths were stamped eight times and had been used to clean the buttocks of the children. The new linen had been stamped the previous day and placed in a separate compartment so that it could be laundered. That night with a change of nursing personnel these cloths were discovered and used. New towels had also been freshly stamped, but no evidence of their use could be found.



Fig. 3 —B. T. (Case 3). Roentgenogram taken March 2, 1945

CASE 4.—The first patient, W. J., noted to be cyanotic, was a 3-week old infant who weighed 5 pounds and 5 ounces. He had been admitted nine days previously because of diarrhea. His weight had increased but he was having four or five watery green stools daily. During the time the freshly stamped washcloths were being used, his buttocks had been washed four times. He also received an oil bath that morning.

At 8 A.M. this child's lips were noticed to be grayish blue and the skin had a bluish tint. There was no respiratory distress and examination of the heart and lungs was normal.

Eight hours later the cyanosis was very marked and, although no respiratory distress was present, the child was placed in an oxygen tent. There was slight improvement, but four hours later the cyanosis was still severe. At this time 2 mg. of methylene blue in 10 c.c. of normal saline were given intravenously. Recovery was dramatic and within one hour the cyanosis had entirely disappeared. After administration of the methylene blue, the patient was removed from the oxygen tent. The cyanosis did not reappear. There was no reduction found in the red blood cell count or hemoglobin; a blood specimen taken during the cyanotic period revealed methemoglobin.

The child showed no apparent ill effects from the aniline intoxication but the diarrhea continued and the patient died one month later. At autopsy he was found to have small ulcerations of the large bowel, hemorrhagic areas in the pancreas, and an acutely inflamed appendix.

CASE 5.—The second patient, J. M., was an infant 2 months of age who had been admitted to the ward nine days previously because of diarrhea. His weight was 8 pounds and 13 ounces, and he was having about four loose stools a day. This patient was noted to be cyanotic about 9 A.M., but the cyanosis was not marked and disappeared about twelve hours later. No treatment was necessary. No other abnormalities except excoriation of the buttocks were noted. The red blood cell count was 3,440,000 per cubic millimeter, with hemoglobin 11.5 Gm. per 100 c.c. of blood. He gradually improved and suffered no apparent injury from the aniline dye.

CASE 6.—The third patient, W. H., was an infant 3 months old who weighed 7 pounds and 15 ounces. He had been admitted to the isolation ward twenty-two days previously because of severe diarrhea. During the time the freshly stamped washcloths were being used, this patient's buttocks were washed three times. The cyanosis was not discovered until 7 P.M. the night of September 15, which was about eleven hours after the appearance of the first case. Physical examination showed a dehydrated and undernourished white male whose lips, skin, and mucous membranes were cyanotic. No abnormality of the heart or lungs could be found. The buttocks were excoriated. No respiratory difficulty was present. During the night the cyanosis became more marked but gradually disappeared the following afternoon. A transfusion of 75 c.c. of citrated blood had been given on September 15, and the red blood cell count was 3,940,000 per cubic millimeter and hemoglobin 13.5 Gm. per 100 c.c. of blood. Blood taken from the patient during the period of cyanosis was chocolate colored. No treatment was instituted and the cyanosis was present about twenty-four hours.

The patient continued to have diarrhea and expired twenty-one days later. At autopsy the cause of death was found to have been peritonitis involving the spleen and the descending and sigmoid colon.

DISCUSSION

Graubarth and associates¹ reviewed the literature, chemistry, and symptoms of aniline poisoning, and reported seventeen cases which developed in a hospital nursery. In their review of the literature they cited five series of cases, with a total of forty-one patients, of aniline dye poisoning reported by five authors (Raymer, Seligs, Weinberg, Newland, and Ewer). All cases were in infants who had been clothed in freshly stamped linens.

In the first episode herein reported, it is interesting to note all the premature infants were affected, but the full-term babies showed only transient cyanosis. Since the premature infants were affected first, one might think they were more susceptible to the aniline intoxication. However, it may be possible that they were diapered earlier with the aniline stamped linens.

In the second episode the three infants affected had diarrhea with excoriated buttocks. These infants did not wear the freshly stamped linens but

were bathed with the washcloths which were newly stamped by the aniline dye. Wetting and wringing out of these cloths caused the water to turn black.

It is interesting to speculate as to the precipitating factors in the latter group: excoriated buttocks, nutritional disturbance, increased absorption of aniline through the skin due to persistent diarrhea or unknown causes.

Another interesting fact is that three of the affected infants died. In the first group it is possible that the aniline intoxication may have been a factor in the death of one premature infant. In the second group of infants, both deaths occurred at least three weeks later and post-mortem examination revealed the causes of death.

In normal times these two accidents would probably not have happened but, as has been pointed out by others,¹ the hospitals have been confronted with many trying situations such as shortage of diapers, inexperienced help, and frequent turnover of employees. This hospital is no exception.

CONCLUSIONS

1. Two episodes of aniline intoxication are reported. One infant was treated with methylene blue intravenously and recovery was dramatic. Cyanosis, which was most marked in this case, disappeared in one hour as contrasted to the others in this series who remained cyanotic from twelve to twenty-four hours.

2. All hospital linens marked or stamped with an aniline dye should be laundered before use.

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A CASE OF TETRALOGY OF FALLOT WITH ABSENCE OF CEREBELLAR VERMIS; TERMINATION BY BRAIN ABSCESS*

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NAVAL RESERVE, AND LIEUTENANT COLONEL M. M. KESSLER, AND
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EIGHTY-SIX authenticated cases of the tetralogy of Fallot had been reported by July, 1941. The full exposition of our case adds to the understanding of the mechanics of this syndrome and records the rare congenital anomaly, absence of the cerebellar vermis.

Peacock¹ first described the tetrad in 1858. In 1888, Fallot designated it as the commonest form of cyanotic congenital heart disease, and it has borne his name since. The tetrad consists of the following four abnormalities: (1) stenosis of the pulmonary valve or stenosis of the pulmonary conus, (2) inter-ventricular septal defect, (3) a dextro-position of the aorta, (4) hypertrophy of the right ventricle.

CASE REPORT

Our patient, a 6-year-old boy, was first seen by us in 1936. Born a blue baby, his condition had long since been diagnosed congenital heart disease without further effort to more sharply define the type.

His appearance was that of a ghastly caricature. An overly large head surmounted a spindly body. A bulbous blue nose stood out on the wizened face. There was a generalized acrocyanosis involving the forearms almost to the elbows and the legs to just below the knees. The color of the nails was purest sky blue untainted by red. The tips of the fingers and toes were moderately clubbed. The boy walked and stood with feet wide apart.

His foster mother, although accepting the diagnosis of congenital heart disease, came to us because she refused to recognize the tiredness and inability to gain weight as part of the picture.

At examination the patient, although cooperative, was slow in his responses. He was often querulous (as if from fatigue). The heart rate was 130 and regular; the sounds were normal except for a second degree, pulmonic systolic murmur. Clinically, the heart was not enlarged; there was no evidence of an endocarditis and none of failure, unless it were in the full veins. The blood pressure was 64/50 in both arms.

The patient was checked every two months as a matter of routine. He was seen through a mild bout of chicken pox and through several respiratory infections. The pulmonic, systolic murmur, while varying from second degree to fifth degree, remained predominantly second degree. On several occasions a superimposed whistle was heard over this same pulmonic area.

In early February, 1938, the patient complained of a dull pain over the upper left precordium on exertion. This pain radiated into the left shoulder. At the onset of the pain, the boy would fall into the nearest chair and remain there until it had vanished. At this juncture a teleroentgenogram and an electrocardiogram were taken.

The heart shadow was within normal limits. The electrocardiogram (Fig. 1), however, revealed an extreme right axis deviation, a sinus tachycardia of 135, an abnormally high voltage of the QRS complexes, and an exaggerated P₂. S-T₂ was depressed. While compatible with the picture of congenital heart disease and right-sided strain, there was nothing clearly diagnostic of active coronary disease. However, the precordial pain continued to recur with ever-increasing intensity. In mid-March it was complicated by loss of consciousness.

*Title suggested by Maude Abbott in personal communication.
Reported at Clinic of American College of Physicians, Cleveland, Ohio, 1940.

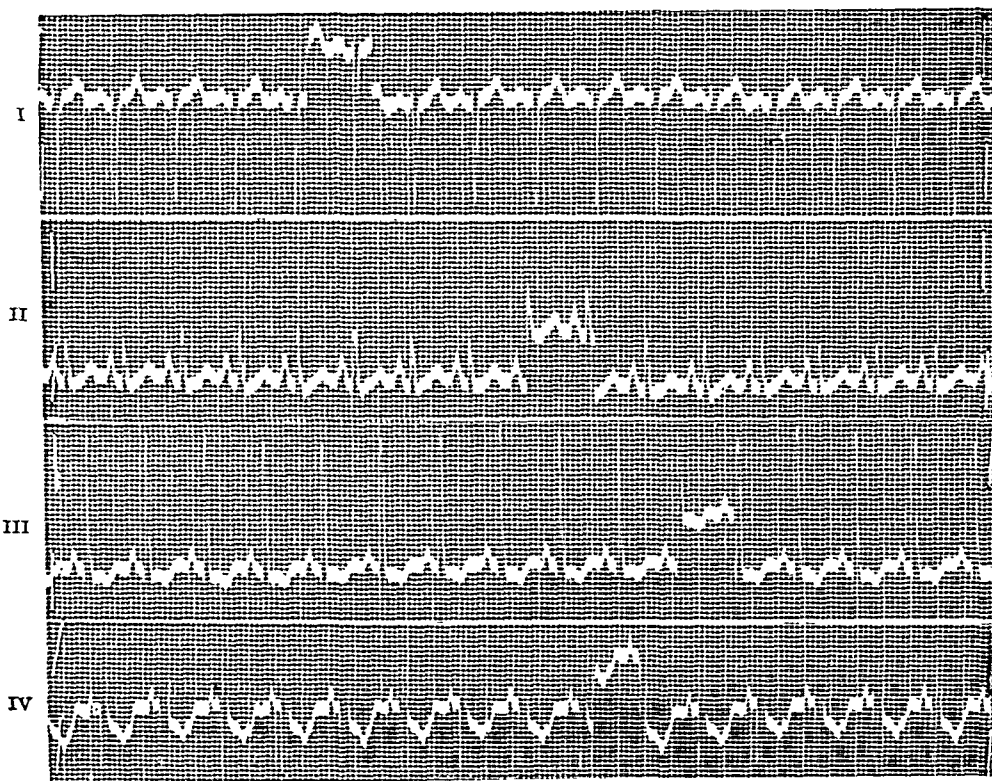


Fig. 1.—Electrocardiogram, February, 1938. Standard limb leads and old Lead IV.

While unconscious, the skin was pale and cold, the heart rate 160 and regular, the pulse thready. The period of unconsciousness varied from one-half to one hour. Though waking free of pain, the patient would recall with fear the initial intense precordial distress. Laboratory findings on March 25, 1938, were 6,500,000 red blood cells and 90 per cent hemoglobin (Sahli). The blood showed a 74.5 per cent oxygen unsaturation. Another sample two weeks later revealed a 66 per cent oxygen unsaturation of the blood.

In May, 1938, oxygen therapy² was first employed for the loss of consciousness. Given in full strength through a mask, its effect was a happy one. The patient now regained consciousness in from five to ten minutes and once, when his mother reached him at his first cry of pain, oxygen aborted the pain as well as the expected syncopal attack within two minutes.

Fluoroscopy on Dec. 1, 1938, again showed the heart to be within normal limits and an electrocardiogram taken the same day showed no significant change from the February tracing. Although increasingly short of breath, the patient voiced no new complaints until May 15, 1939, when he complained of a severe headache. The temperature was subnormal and the neurological examination negative. Tending from the first to explain all signs and symptoms on the basis of congenital heart disease alone, we mistakenly ascribed the headache to an increasing hydrocephalus due to an elevated venous pressure. When, therefore, dehydration measures provided temporary relief from the headache, we were more than ever convinced of this assumption. The patient grew listless. His breath was fetid. The gums and cheeks now showed a full-blown gangrenous stomatitis.

On June 2, 1939, a sudden rise of temperature to 103° F., a meningeal cry, a rigid neck, and a spasticity of the right arm and leg first roused us to other possibilities. With the mother invoking death as a blessing, all diagnostic procedures were held in abeyance. The

next day, June 3, 1939, the right arm and leg were completely paralyzed and early papilledema of the left optic disc was noted. The patient expired that evening.

An autopsy performed by Drs. B. S. Kline, Anna M. Young, and one of us (R. W.) revealed numerous congenital abnormalities. In passing, mention is made of three left and two right renal arteries as well as of adhesions between the large and small bowel. The cardiac findings follow: The right auricle was dilated to three to four times the size of the left, and the right ventricle was dilated to the point where it, too, was larger than the left.

The heart weighed 95 grams.

Tricuspid ring circumference	7.0 cm.
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Pulmonary ring circumference	4.5 cm.
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Mitral ring circumference	6.0 cm.
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Aortic ring circumference	5.0 cm.
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These measurements were considered normal for the age. The valve leaflets appeared normal and were fully competent.

Length of right ventricle	6.0 cm.
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Length of left ventricle	5.0 cm.
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Thickness of right ventricular wall	4-10 mm.
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Thickness of left ventricular wall	8-12 mm.
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Fig. 2—Base of brain showing absent olfactory tracts and perforation in the floor of the third ventricle.

There was a defect of the anterior superior interventricular septum measuring 6 cm. in circumference and the aorta, dextroposed to the right, rode over the defect, so that it opened half into the right ventricle and half into the left. While the pulmonary valve was normal, the pulmonary conus beginning just above it and extending upward for 1.5 cm. was constricted to a slitlike channel not over 2.1 cm. in circumference. This channel was further encroached upon by grayish-red vegetations of as much as 3 mm. in diameter. The coronary arteries, dissected to their terminal branches, were patent throughout. Cultures, both of the blood and of the vegetations themselves yielded no growth. Microscopic sections of the myocardium revealed areas of hypertrophy of the cardiac musculature as well as areas of scarring and replacement of the myocardial fibers by relatively acellular fibrous tissue. On the whole, the greatest hypertrophy was subendocardial, whereas the areas of degeneration were subepicardial.



Fig. 3.—Superior view of cerebellum showing absent vermis. The floor of the fourth ventricle is accordingly seen between the lateral hemispheres.

The brain findings follow: The brain was larger than average weighing 1,360 grams. A number of anomalous conditions presented themselves. There were several fenestrations in the falx cerebri. The anterior half of the corpus callosum was absent. Thus, the lateral ventricles presented themselves as indentures from the medial surfaces of the cerebral hemispheres. There was an oval defect in the floor of the third ventricle measuring 1 cm. in greatest diameter (Fig. 2). The cerebellum presented itself as two widely separated lobes due to the absence of the vermis (Fig. 3). The fourth ventricle, accordingly, had no roof and was, in reality, a huge cisterna. The olfactory bulbs and tracts were totally absent (Fig. 2).

The left cerebral hemisphere was considerably larger than the right, and in the left parietal region there was a soft, fluctuant area which was friable and ruptured on slight manipulation. Thick, yellow mucus was obtained from this opening. Similar purulent material was found in the left lateral and third ventricles. The surface vessels over the cerebral convexities were markedly injected. The venous sinuses were greatly dilated. There was a depression of the calvarium corresponding to the position of the lateral sinuses, measuring 2.5 cm. in diameter. The middle ears, and the sphenoid and ethmoid sinuses showed no gross abnormalities.

The brain was cut coronally after formalin fixation. In repeated sections, the anterior horn of the right lateral ventricle was found to be absent. Posteriorly, the ventricle was enlarged. A communication between the ventricle and the abscess in the left parietal lobe was demonstrated. Both foramina of Munro were dilated and a large portion of the septum between the third and lateral ventricles was absent. The iter appeared dilated. The pons was considerably smaller than average.

Microscopic examination of blocks of brain removed for study showed the following: There was a portion of abscess cavity with central defect filled with polymorphonuclear leukocytes. The surrounding parenchymatous tissue showed typical degenerative changes. The adjacent arachnoid was distended apparently by edema and was richly infiltrated by wandering cells and small leukocytes. In other sections, the architecture of the cerebral cortex and the cellular morphology showed no deviation from the normal. All other structures appeared normal.

COMMENT

A. The Heart.—From the first we had difficulty in reconciling our meager clinical findings with the accepted picture of the tetralogy of Fallot. Textbook summarizations of the tetralogy usually agree on a loud, prolonged, systolic murmur heard over the entire precordium, a palpable systolic thrill, marked clinical and x-ray enlargement of the heart, and an overwhelming hypertrophy of the right ventricle. Careful perusal of the literature, however, reveals that many of the cases varied widely from this textbook picture. In 15 per cent of the reported cases the authors failed to note even a systolic murmur while a much larger group noted only a faint murmur. Theoretically, all cyanotic congenital heart diseases (with the exception of the rare cor triloculare), based as they are on a fundamental obstruction to pulmonary flow, should present a marked pulmonic systolic murmur. Our problem is concerned, therefore, with explaining the failure of our case and others in the literature, to meet the expected picture of the tetrad.

Such an explanation is offered in the graphic diagrams (Figs. 4 and 5) which depict the two extremes of anatomic variation in the tetrad.

While the final word on the causation of murmurs has yet to be said, Lewis, Best and Taylor, and White are fully agreed that the rate of flow is a predominant factor therein. Quoting White³: "If the flow is fast, the murmur will be louder; if the flow is slow, the murmur may become fainter, and if the flow is very slow, the murmur may disappear altogether."

We have observed this same phenomenon in a patient with a button-hole mitral stenosis. The fixation of the valve leaflets, one to the other, verified at autopsy, precluded any widening of the mitral orifice due to dilatation of the ring. Yet, during three acute illnesses, we observed the harsh apical diastolic murmur and thrill vanish, only to recur with the subsidence of the disease as the heart thrust grew in power and the rate of blood flow increased.

Bearing this in mind, the significance of the arrowheads indicating the rate of flow takes on new meaning in Figs. 4 and 5. In Fig. 5 we see illustrated the textbook version of the tetralogy with only a small septal defect. By far the greatest rate of flow (we have chosen an arbitrary three-quarters for purposes of illustration) is through the narrowed pulmonary orifice or conus, resulting in a marked systolic murmur and even thrill. Under the continued strain of expelling blood through a narrowed orifice, the right ventricle has hypertrophied markedly. Contrarily, the cyanosis (as noted in 40 per cent of Abbott's⁴ series) is not marked since only one-quarter of the right ventricular flow is being shunted to the left.

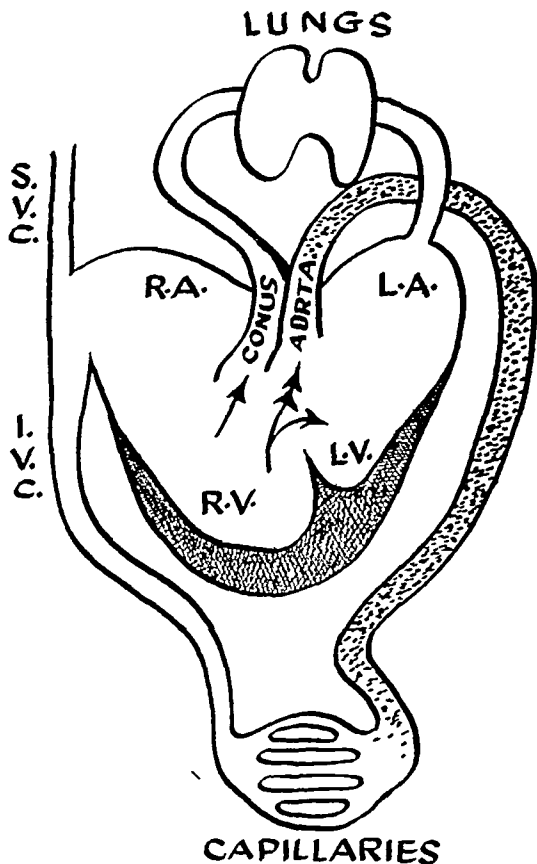


Fig. 4.—Large septal defect. Marked cyanosis. Faint to moderate systolic murmur. X-ray evidence of enlargement not requisite. Note moderate hypertrophy of wall of right ventricle. Number of heads on arrows denotes proportionate rate of flow from right ventricle.

By comparison, the very wide septal defect (in our case seven times as large as the stenotic pulmonary conus) (Fig. 4) results as the arrowheads show, in a diversion of three-quarters of the right ventricular blood flow either into the left ventricle or directly into the aorta. Hence, the remaining one-quarter of the flow through the pulmonary orifice, falling under the "slow" or "very slow" rate of flow referred to by White, is incapable of producing more than

a faint systolic murmur. Further, while this very shunt of three-quarters of the right ventricular blood flow to the left is producing an extreme cyanosis, it is at the same time relieving the right ventricle of much of its pulmonic back pressure. Viewed in this light, a moderate hypertrophy of the right ventricle is all that is to be expected. Heretofore, the cyanosis out of proportion to the right ventricular hypertrophy has been explained away on the basis of a decreased rate of capillary flow resulting from low arterial pressure (Wiggers⁵). With our conception, it is no longer necessary to rely solely on such an explanation of the seeming paradox of extreme cyanosis and only moderate right ventricular hypertrophy.

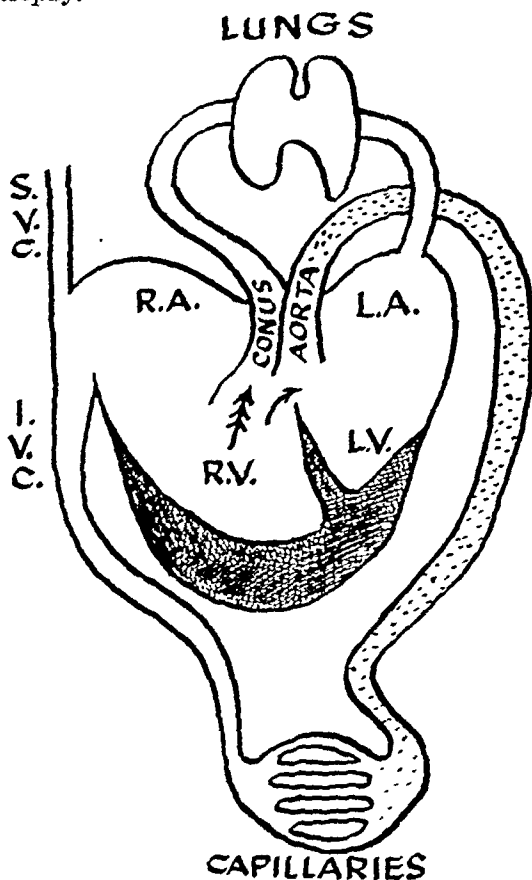


Fig. 5.—Small septal defect. Less extensive cyanosis. Systolic pulmonic murmur and thrill. X-ray enlargement of right ventricle. Note extreme hypertrophy of wall of right ventricle. Number of beads on arrows denotes proportionate rate of flow from right ventricle.

When the autopsy failed to reveal any evidence of coronary disease, we were faced with the task of explaining away both the angina and the minute areas of myocardial degeneration hitherto associated only with capillary thrombosis.

Though it is far from our purpose to enter into a discussion of the various theories regarding angina and myocardial infarction, we cannot refrain from

noting that our case lends support to the dominant role of anoxemia in the production of both.

Thus, while some would insist that cardiac pain is initiated by an accumulation of metabolic (waste) products irritating the afferent nerve fibers of the myocardium, Katz⁶ has emphasized the converse of this statement. Since oxygen is a prime requisite for the conversion of these irritative metabolites into non-irritative substances, he points out that no such accumulation is possible in the presence of an unlimited supply of tissue oxygen. Conversely, the irritative substances accumulate wherever there is tissue anoxia, because the oxygen lack halts or slows the conversion of these metabolites.

Smith and Gault⁷ in a similar vein, have pointedly referred to the role of anoxemia in myocardial infarction. In those instances in which coronary occlusion did not lead to immediate death, they state: "It results in a localized anemia of the heart muscle and is accompanied by all the degenerative changes associated with anoxemia."

Our patient with his normal coronary flow, with his normal blood count, and, to the best of our knowledge, with other constituents of the blood normal, constituted an excellent situation for the study of the effects of severe anoxia alone upon the heart. The degree of cardiac anoxemia could be determined from the microscopic sections. These showed focal degeneration of cardiac muscle subepicardially and muscular hypertrophy subendocardially. Hence the assumption might be drawn that the subendocardial layer had an accessory oxygen supply. The anatomic presence of the thebesian vessels which traverse the innermost muscle layers offers the only convenient means for an added oxygen transport to the subendocardial layer. That the little oxygen derived from the admittedly small thebesian flow should be the deciding factor between a hypertrophying subendocardial layer and a degenerating subepicardial layer but emphasizes the critical oxygen lack of the cardiac muscle.

In this case, where there were no technical means for measuring the oxygen values of cardiac muscle, these anatomic data serve as the only available index of the extent of oxygen lack. This cardiac anoxia must have been the maximal amount compatible with heart function. The study of this case has given us a physiologic basis for the presence of both angina and tissue degeneration in the absence of coronary obstruction.

The effectiveness of the oxygen therapy is no longer surprising in view of its critical need.

B. The Brain.—The most striking of all the anatomic variations in this brain was an aplasia of the cerebellar vermis. Clinically, however, all that was noticed in the patient was a wide-based gait and stance and a tendency to posture the head backward. This picture falls far short of the flocculonodular syndrome described by Botterell and Fulton⁸ after experimental lesions in primates. Yet, the persistent, wide-based gait does identify it with this syndrome. Neural compensatory mechanisms were undoubtedly called into play as the child learned to sit up, balance, and finally walk. Accordingly, the neurological picture of this defect became obscured. The reduction in the size of the pons is in proportion to the absence of cerebellar substance.

Absence of the cerebellar vermis is a rare anomaly. Only two cases, both described by Solovtsoff,⁹ were mentioned in a recent review¹⁰ of cerebellar agenesis. Baker¹¹ described one case in which the cerebellum was totally absent and another in which one of the cerebellar lobes was absent.

In analyzing the absence of the olfactory bulbs and tracts, we are confronted with yet another paradox. The child's mother insisted that he frequently would ask to go into the garden, so that he might smell the flowers. Nevertheless, in the face of anatomic proof, the conclusion must be drawn that the child's mother was either mistaken in her statement or misunderstood his mimicking of other persons' reaction to flowers as the act of smelling.

In the presence of so many anomalous conditions in the brain, it is not surprising to find an associated hydrocephalus. There were at least four situations where ventricular fluid communicated directly with the subarachnoid space. Derangement of flow of cerebrospinal fluid could, of itself, so alter the hydrodynamics within the skull, that a hydrocephalus would result. However, there is another factor which must be considered in the pathogenesis of the hydrocephalus. The chronic elevation of venous pressure as manifested by the great and persistent dilations of neck veins, during life, and the enlarged venous sinuses within the cranium at autopsy, may have been the basis for an increase in cerebrospinal fluid pressure. The presence of increased intracranial pressure before closure of the fontanel, can produce an enlarged skull. In all probability, the hydrocephalic head was due to a combination of these factors. It is to be noted that an Arnold-Chiari deformity was not present in this case.

The origin of the brain abscess which proved to be the proximate cause of death, was undoubtedly embolic. Abscess by contiguity was practically ruled out by the findings in the autopsy that all the cranial air sinuses were uninfected. The vegetations on the heart valves were naturally to be considered as a source of the embolus. However, all indications pointed away from this possibility. First, the vegetations were in the pulmonary stream and thus would be filtered out in the lungs. Second, the vegetations appeared to be in the process of healing and were described as chronic verruca. The chance of emboli being released from the vegetations was, therefore, minimal. The absence of pulmonary embolization would tend to substantiate this contention. Third, *Streptococcus viridans* was not recovered in the culture of the brain abscess or the cardiac vegetations. The absence of the usual organism associated with subacute bacterial endocarditis is significant. Lastly, it is very unlikely that the three pyogens, *Staphylococcus aureus*, *Bacillus pyocyaneus*, and *Bacillus coli*, actually cultured from the abscess, would all be present in the vegetations on heart valves.

We must, therefore, look elsewhere for a source of the infected embolus containing these three common organisms. The clinical record gives the clue. The patient had a severe mouth infection, with gingivitis. During the course of severe gingival infections, emboli are known to pass from thrombophlebitic veins to the pulmonary circulation (Kline and Berger¹²) and are sometimes the source of lung abscess. These oral infections are due to mixed invaders.

The cardiac anomaly affords the anlage for the venous embolus avoiding the pulmonary circulation and passing directly into the systemic circulation. In this case, in which probably three-quarters of the blood from the great veins was shunted through the interventricular septal defect to the systemic circulation, an infected embolus from the oral region could easily find its way to the brain creating an abscess. It is therefore felt that the brain abscess resulted from paradoxical embolization, the source of which was a badly infected mouth.

This case with its combination of rare cardiac and cerebral anomalies has been a challenge to our conceptions of bodily function. Adequate workup of other such anomalies as may be seen from time to time may well further our knowledge of physiology.

SUMMARY

1. A case is presented of multiple congenital anomalies, the outstanding ones being a tetrad of Fallot and an aplasia of the cerebellar vermis. Exitus was by cerebral abscess.

2. The principal clinical features were: a profound acrocyanosis, bouts of angina complicated by syncope, and cardiac signs which were surprisingly minimal. The patient also presented a hydrocephalic head and moderate signs of cerebellar dysfunction.

3. The principal anatomic findings were: the expected tetrad of Fallot, a healing verrucous endocarditis of the pulmonary conus, a cerebral abscess, and multiple anomalies of the brain, the striking feature of which was an absence of the cerebellar vermis.

4. Explanation is offered for the disparity between clinical signs and anatomic findings in the heart. The pathogenesis of the brain abscess was shown to be an instance of paradoxical embolization.

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CONGENITAL HEMANGIOMA OF THE PAROTID GLAND

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TUMORS of the parotid gland have been described and discussed many times in the literature. It has been our observation, however, that only tumors in adults were adequately described and that congenital tumors were usually mentioned only in a casual way.

Hemangioma or hemangioendothelioma of the parotid gland is one of the rarely mentioned congenital tumors. A description of the tumor, with a personal observation by one of us (K. G.) in *L'Hémangiome de la Parotide*, was published in 1939.¹ After that year there is scant literature on these congenital tumors with only occasional and incomplete mention of their clinical course and prognosis, which, as seen in our case, is of utmost importance for the treatment and subsequent life of the patient.

Judging by the scarcity of the literature, the tumor must be of rare occurrence. In the published cases the majority of the tumors occurred in female children and most of these were situated on the right side.² The main diagnostic features are the presence of the tumor at birth or its appearance during the first weeks of life; the unilateral occurrence; the enlargement of the tumor on crying; the elastic consistency, the compressibility, and the lobulation felt upon palpation. The skin covering the tumor may be either normal in appearance or show bluish discoloration, may include a hemangioma, a telangiectasis, or an increased venous design. Signs of inflammation and pain or tenderness are absent in uncomplicated cases.

The tumor takes a rather characteristic and uniformly disastrous course. It usually grows slowly in the beginning, but suddenly, even without any apparent outside stimulation, the speed of its growth increases until the death of the patient, within a few weeks or months, due to invasion and compression of the vital organs of the neck. If surgical intervention occurs, the course is changed considerably. If surgery is radical and all parts of the tumor are removed (this may necessitate trauma to or destruction of a portion of the facial nerve) the prognosis for a permanent cure is favorable. In the cases in which the operation has *not* been radical, either because only a diagnostic biopsy has been performed or because of the fear of injury to the facial nerve, the remaining portion of the tumor continues its growth at a much accelerated pace and the death of the patient is usually hastened. The success of a second operation is usually questionable because of the far-reaching invasion of the surrounding tissues and organs, including the vital blood vessels of the neck.

Microscopic findings which have been reported have been uniform in the description of the types of tissue found. Capillary, cavernous, and endotheliomatous types have been described. Under low magnification there is an al-

From The Children's Memorial Hospital and The Otho S. A. Sprague Memorial Institute.

most homogeneous mass of nuclei. Fibrous septa separate the tissue into a lobulated structure. Under higher magnification a new tissue of vascular nature is seen which replaces large portions of the normal parotid gland. Numerous small capillaries are present, many filled with red blood cells. In some areas the capillaries are collapsed and the tissue has a densely cellular appearance. When the tumor invades the parotid tissue there is a more rapid diminution or replacement of the secretory part as compared with the excretory portion. Invasion of the surrounding tissues is by continuity. No mitotic figures are seen.

CASE REPORT

B. C., a 2½-month-old female child, was admitted to The Children's Memorial Hospital on Dec. 12, 1944. The complaint on admission, as given by the mother, was a swelling of the right cheek, which was first noticed at the age of 2 weeks by an aunt of the child. The swelling was so small that it did not cause any concern until the child had reached the age of 6 weeks. There was never any apparent distress occasioned by the swelling, and the child had never shown any signs of illness. Rapid enlargement, redness, or tenderness of the mass had never been present. Birth history, feeding history, and developmental history were normal. The family history was irrelevant. Physical examination revealed a well-nourished, white female child showing no abnormalities other than a sausage-shaped mass the size of a half-dollar located in the right parotid area. This had no apparent connection with the covering skin or underlying bone. The mass could not be transilluminated, was slightly lobulated and elastic to palpation. The skin over the swelling had a slightly blue tinge.



Fig. 1.—Portion of tumor with dilated capillaries.

Because of an upper respiratory infection which developed, the child was discharged and later readmitted to the hospital on Jan. 11, 1945, and operated upon the following day by one of us (L. W. S.). Under ether anesthesia a tumor, 1.5 by 2.5 cm., was removed through an incision paralleling the branches of the facial nerve. The capsule of the tumor was adherent to the surrounding tissues; the base from which it sprang was very deep seated and buried in the parotid gland. A few small branches of the facial nerve were dissected from the tumor and the mass was removed along with a small portion of the parotid tissue. The postoperative course was uneventful.

On March 15, 1945, the child was readmitted to the hospital because of a recurrence of the mass. The following day an operation was performed (two months after the first),

and through the original incision a wide, sharp dissection was employed, with removal of the tumor mass and the adjacent portions of parotid tissue. Several branches of the facial nerve had to be destroyed or stretched rather severely to gain access to the tumor for its removal at this time.

Following the second operation the child received twelve roentgen ray treatments to the right parotid area. The essential factors were filters of $\frac{1}{4}$ copper and 1 aluminum, using 130 peak kilovolts; 5 milliamperes. The average dose was 170 r at intervals of one week. The postoperative course was uneventful and seven months later there was no evidence of recurrence. There are definite signs of right facial paralysis which were more pronounced immediately after the operation, but still are and most likely will be permanently perceptible.

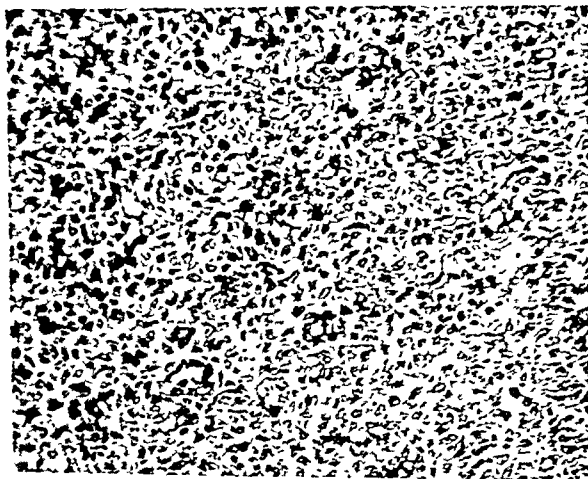


Fig. 2.—Markedly cellular portion of tumor with collapsed capillaries.

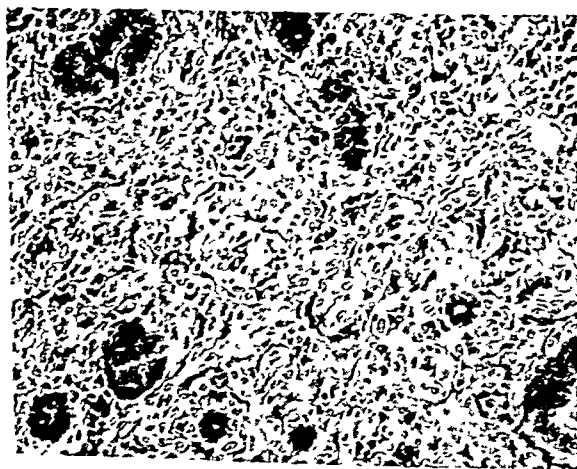


Fig. 3.—Replacement of parotid gland by tumor with only ducts remaining.

The surgical specimens were similar on both occasions. The total mass of tissue received following the second operation weighed 11 grams, the first was not weighed. The tissue was lobulated, semifirm in consistency, and was

surrounded by a rather tough capsule. The color varied from a fatty yellow to a muscle red. No necrosis or cysts were seen grossly. A small nerve was found passing through the largest mass of tissue. Microscopic examination showed salivary tissue in which there was partial or total replacement by vascular tissue. Vascular spaces were numerous (Fig. 1) and many contained red blood cells. In some areas the capillaries were compressed, giving the appearance of densely packed endothelial cells (Fig. 2). The endothelial cells varied considerably in size and shape, had a rather pale cytoplasm, and, except in limited areas where the cells were arranged in fascicles or whorls, assumed no definite polarity. Where there was only partial replacement of the parotid tissue the acinar portion was absent, but ductal tissue was present in moderate amounts (Fig. 3). A few small nerves showed invasion by the tumor tissue. Some areas of the tumor showed good encapsulation. No mitotic figures were seen.

SUMMARY AND CONCLUSION

A case of congenital hemangioendothelioma of the parotid gland is reported. The clinical and pathologic findings as well as the surgical procedures have been described.

The important conclusion to be drawn from the observation of this case and the investigation of the literature is of diagnostic, therapeutic, and prognostic significance. The contrast between the benign appearance of the tumor both macroscopically and microscopically and the highly malignant clinical course is most remarkable. The treatment recommended is the total extirpation of the tumor, sacrificing the facial nerve and parts of the parotid gland if necessary, followed by radiation therapy. If the operation has been early and radical the prognosis is favorable.

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A PRACTICAL URINE OR WET DIAPER SIGNAL

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IN 1904, Pflaundler¹ described a device of tinfoil separated by cloth connected to batteries and an electric bell. At first Pflaundler used the device under enuretic children as a wet diaper signal, but soon he discovered that if the device were used continuously under a child for a month or so, the ringing of the bell had therapeutic results. In many cases the knowledge alone that urination in bed would cause a bell to ring seemed to inhibit the act.

In 1908, Genouvill² and in 1910, Rémy-Roux³ published papers describing the use of Pflaundler's method which they reported as giving good results. However, the method did not come into general use. Probably the main handicap was that the crude design of the devices made their use very complicated. The Pflaundler pad consisted of two pieces of wire screen separated by a removable piece of linen. A relatively large amount of urine had to pass through the pad to make the bell ring. Rémy-Roux used a layer of absorbent cotton in place of linen.

In 1938, Mowrer⁴ improved the Pflaundler apparatus by placing a relay in the pad circuit, thus making it sensitive to smaller amounts of urine; they further improved the pad by permanently quilting the metal screens. These changes made the apparatus function more quickly before the pad became completely wetted, which is desirable.

With this apparatus Mowrer and Mowrer⁵ obtained excellent results in a group of thirty children ranging from 3 to 13 years of age. Enuresis was eliminated in all cases. The maximum time required to accomplish this in any child was two months. The promptness of the therapeutic effect depended on the age of the child, his eagerness to overcome his difficulty, and a number of variable factors. One feeble-minded child with an I.Q. of approximately 65 responded satisfactorily.

There have been other similar devices reported in the newspapers and periodicals without descriptions of any therapeutic advantages.

On May 4, 1936, the *Baltimore Sun* printed the following: "Svorillovsh, USSR Russian Science, has just announced to Soviet Motherhood a light which flashes when baby needs changing. Wires from batteries are attached to strips of tinfoil in a special packet beneath the tinfoil. Cloth sandwiched between the tinfoil becomes a conductor when dampened and, presto, the light goes on. The system is already in use in a hospital here."

In 1930, a device which required several pounds of salt to be replaced every time the pad was wetted was given a patent by the patent office.

All of these devices have one common fault. They consist of two conductors separated by an *absorbent nonconductor* which, once it becomes wet, is a conductor and has to be replaced or dried, or washed and dried, because of the odor and inoperability of the pad when wet.

The best of these pads is that devised by Mowrer. However, in his instructions it is recommended that several pads be kept on hand and that after each use they be thoroughly dried, preferably in the sun, before being used again.

The device to be described here overcomes all these disadvantages. It is probably even more sensitive than Mowrer's device, because wetting one-half square inch of the pad will cause the bell to ring. Since the pad is made only of rubber and metal, it has no absorbent media and therefore does not have to be dried. Only one pad is necessary for each patient and this pad will last indefinitely. There is practically no objectionable odor from the pads as they are made of rubber and metal with a smooth surface which can be wiped or washed like a rubber sheet. In practice, a diaper is placed over this pad with the bare buttocks resting on the diaper, or the diaper is pinned over the pelvis in the usual manner and the diaper-covered buttocks rest on the pad. In either case, as soon as the wet diaper is lifted off the pad, the bell stops ringing. If there is a pool of urine on the pad simply wiping the top of the pad with a dry end of the diaper makes the pad ready for use again immediately.

The simplicity of its use makes it adaptable as a wet diaper signal when it is desired that the baby's diaper be changed as soon as possible after wetting. While this is routinely desirable it may be especially so when the infant has a diaper rash due to an irritating urine, or if the infant is suffering from any other skin abnormality which contact with urine would aggravate.

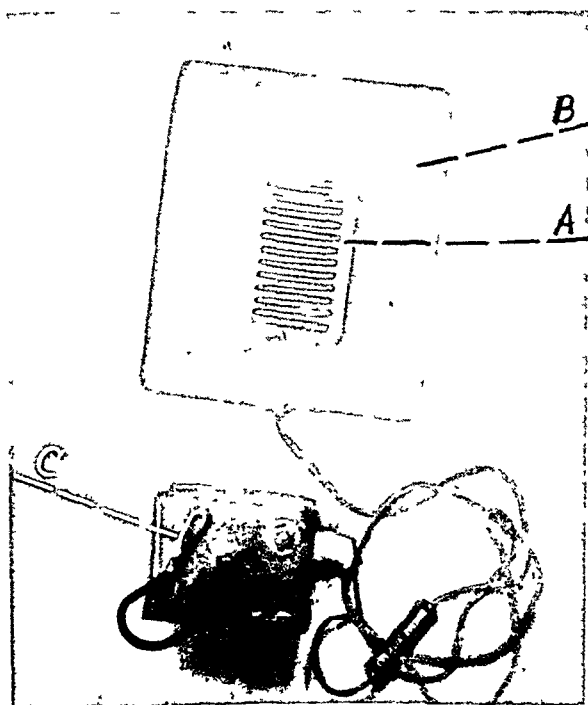


Fig. 1.—A, metal grid; B, rubber pad. C, box containing batteries, relay bell, and switch

Many other possibilities suggest themselves. It may be used under the buttocks of the incontinent in the presence or absence of decubital ulcers. After a cystostomy it will signal when the tube is blocked off and there is a leakage around the tube in the cystostomy wound.

Since all body fluids contain sufficient electrolyte to operate the device, it may also be used under a patient with a draining gall bladder to signal when there is leakage around the tube in the cholecystostomy wound. Along this line other uses may suggest themselves.

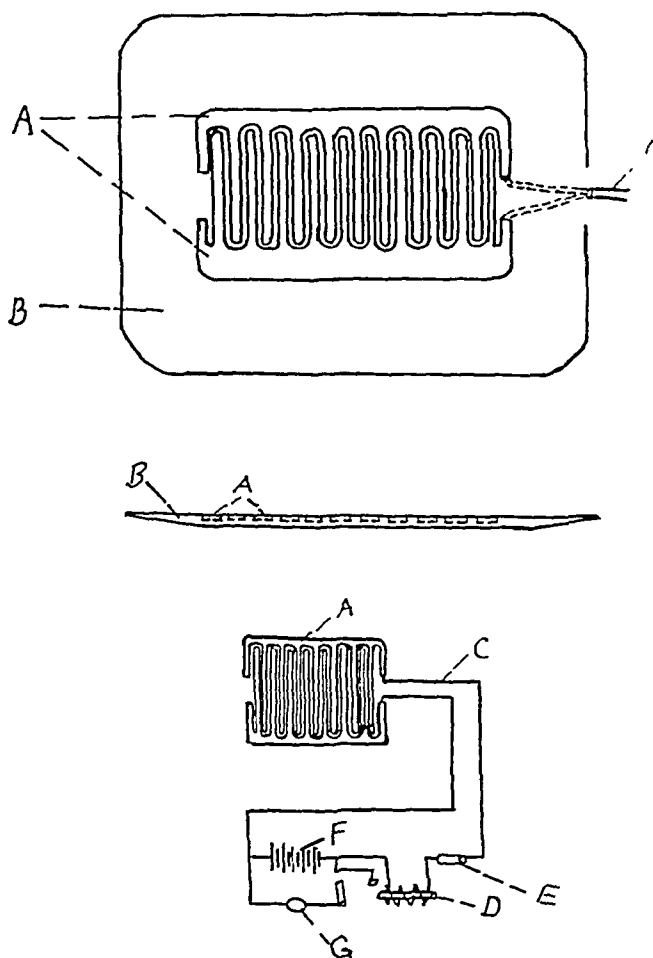


Fig. 2.—A, metal grid; B, rubber pad; C, connecting wire; D, relay; E, switch; F, batteries; G, buzzer or other signal.

Fig. 1 is a picture of the device. Fig. 2 outlines its electrical circuit. The device has been made with a light signal instead of a bell in cases where a visual signal would be preferable to an auditory signal, as in a hospital.

The metal grid (A in Fig. 1) used in the device has been made of inconel, a noncorroding nickel chrome alloy. This metal grid is 4 inches by 6 inches in size, and .006 inch thick and is cemented to the rubber pad (B in Fig. 1). To

adhere the metal grid to the rubber pad a cement called Vulcalox* is satisfactory and after vulcanization in a mold, the metal is flush with the rubber, the pad having an over-all smooth surface. The thickness of the pad is $\frac{1}{8}$ inch in the center and it tapers to a thin edge. At the periphery, the edges of the pad measure 12 inches by 18 inches. It is flexible and conforms readily to the contour of the body.

Further manufacturing specifications are: The relay should be a simple relay of 500 ohms. When the pad is used in the treatment of enuresis, a loud bell is provided; but when used as a wet diaper signal in the very small infant or the incontinent, a buzzer is perhaps more agreeable acoustically. The current for the relay and bell is supplied by six flashlight Type D dry cells connected in series. While these cells have to be replaced more often than the larger dry cells, the relatively low cost and ease of replacement make them more desirable. It also makes a compact arrangement, and the customary intermittent use of the device enables these small cells to give many weeks of service before replacement is necessary.

SUMMARY

A device is described, simple in construction and easy to operate, which will signal on contact in the presence of any electrolytic liquid such as urine, bile, or other body fluids.

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*Vulcalox is manufactured by The B. F. Goodrich Company, Akron, Ohio.

Critical Review

ADDISON'S DISEASE IN CHILDREN

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IN RECENT publications, there have been many contradictory statements concerning the number of cases of Addison's disease that have occurred in children under 15 years of age. In addition, the diagnosis of some may be questioned; therefore it was decided that the literature should be scrutinized, in an effort to evaluate each case on its individual merits.

Although Eustachius,¹ in 1563, described the suprarenal glands, it was not until 1849 that Thomas Addison,² before the South London Medical Society, made the first announcement concerning the pathologic changes in the adrenal glands. Six years later, in 1855, he published a book, *On the Constitutional and Local Effects of Disease of the Suprarenal Capsules*.³ He described a train of symptoms that is generally accepted at the present time as indicative of chronic adrenal insufficiency. In this publication, Addison stated: "The leading and characteristic features of the morbid state to which I would direct attention, are anemia, general langor and debility, remarkable feebleness of the heart action, irritability of the stomach, and a peculiar change of colour in the skin, occurring in connection with a diseased condition of the suprarenal capsules."

Of the cases originally described by Addison, six were due to bilateral tuberculosis of the adrenal glands; two cases were caused by metastatic carcinoma involving both adrenal glands; and one was a case of atrophy of the glands. None of these cases occurred in children. Present-day knowledge has very little to add, as far as the symptomatology and etiology are concerned.

In the light of recent discoveries concerning the metabolic disturbances associated with insufficiency of the adrenal glands, it was felt that no reports of patients should be included in the list of proved cases, unless there were evidence either of characteristic blood chemical changes, obvious improvement following adequate therapy over a long period, or autopsy findings demonstrating inadequacy of adrenal cortical tissue.

The symptoms of weakness, anorexia, intestinal upsets, and weight loss are not diagnostic, since any debilitating disease may cause such complaints. Pigmentation of the skin has been described in generalized tuberculosis, chronic nephritis, familial melanoderma, bronze diabetes.

Addison's disease is a clinical and not a pathologic entity. Any process directly or indirectly responsible for destroying the adrenal cortex sufficiently to produce the signs and symptoms described by Addison justifies this diagnosis.

It was not until 1932, that Loeb⁴ demonstrated that the sodium level was low and potassium level high in this disease.

It is realized that many of the cases listed under the probable category may have been Addison's disease, but since knowledge of the physiologic and chemical disturbances and potent adrenal extracts was not available at the time many of these were reported, it was impossible to be certain of the diagnoses without autopsy confirmation.

Following is a summary of each case classified as *proved*:

In 1856, Ogle⁵ reported a case of a girl, 14 years of age, who had clinical findings of active tuberculosis of the lungs, but, in addition had many symptoms

suggestive of Addison's disease. However, there was no pigmentation of the skin or mucous membranes. Autopsy revealed marked thickening of the adrenal glands with replacement of the natural tissue with tuberculous material. In addition, there was evidence of generalized tuberculosis involving the lungs, left kidney, and bladder. This is the first authentic case of Addison's disease in a child with the pathologic findings substantiating the clinical diagnosis.

In 1857, Fernie⁶ described a case of a 14-year-old girl who gradually became debilitated over a period of three years, presenting many of the symptoms and signs of Addison's disease, including peculiar discoloration of the skin. Autopsy revealed active pulmonary tuberculosis of the right lung, and both adrenals were completely replaced by caseous deposits.

In 1858, Hutchinson⁷ presented a case of a boy, 11 years old, who became ill with symptoms and signs of Addison's disease and expired a few weeks later following a series of convulsions. The adrenals were found to be completely destroyed by "cheesy material." In addition there was evidence of generalized tuberculous involvement of the mesenteric glands. Up to this time this was the youngest patient of whom a case is recorded. Hutchinson judged it would take at least a year for the adrenals to be filled with masses of "dry, cretaceous deposits." However, the boy had been perfectly well until a few weeks before his death. Ten days before death, he walked a distance of four miles to and from the hospital.

In 1858, Bennett⁸ reported the case of a boy, 11 years old, tall, thin, emaciated, and with "bronzed" skin for six months, who had been ill for only a few weeks. He walked to and from the hospital a few days before his death. At post-mortem, both adrenal glands were found to be completely destroyed by tuberculous infiltrations. It appears that Hutchinson and Bennett may have presented the same case.

In 1859, Mackenzie-Bacon⁹ described a 15-year-old boy, who had been ill for seven months with anorexia, nausea, weakness, and general pigmentation. Autopsy revealed bilateral tuberculosis of the adrenals and nothing else.

In 1860, Henoch¹⁰ presented a case of a boy, 12 years of age, who had been debilitated for three years. He presented symptoms of marked progressive weakness, chronic cough, periods of vomiting and diarrhea, and he expired following a convulsion which lasted twelve hours. Both adrenals were found to be replaced by calcium and caseous deposits. In addition to the increase in melanin pigment in the skin, there was a generalized bronchial and mesenteric glandular adenopathy with increased pigmentation of these structures. The liver, spleen, and heart were found to be undergoing fatty degeneration.

In 1860, Aldis¹¹ reported a 12-year-old boy, who had been ill for four months, with olive discoloration of the skin, feeble pulse, vomiting, fainting, and incontinence of the bladder. The diagnosis was confirmed by Addison. Post-mortem revealed that only the adrenals were involved, and they were replaced by a firm, caseous material.

In 1861, Barker¹² described a 14-year-old boy, who for four months had experienced pigmentation of the skin, anorexia, vomiting, pain in the abdomen, and gradual emaciation. At autopsy both suprarenal glands were found to have been completely destroyed by tuberculous deposits. There was also a moderate degree of pulmonary tuberculosis.

In 1861, Broadbent¹³ reported a girl, age not given, who had many months of debility, low-grade fever, discoloration of the skin and chorea. At autopsy both adrenal glands showed "scrofulous" deposits, but there were no other significant findings.

In 1861, Montgomery¹⁴ described a case of a boy, 14 years of age, who became ill and expired after a period of five months. He had many of the symp-

toms of Addison's disease. It was found that the adrenals were completely destroyed by tuberculous material and evidence of healing tuberculosis was found in both lungs. The skin showed the usual change in color.

In 1862, Wilks¹⁵ described the case of a boy, 13 years of age, whose condition was diagnosed as this disease by Thomas Addison. This child presented a picture of marked emaciation, incontinence of the bladder, dehydration, marked asthenia, and generalized pigmentation of the skin, of four months' duration. Post-mortem examination revealed no traces of normal adrenal tissue, this being entirely replaced by "tough, yellow amorphous tuberculous material." No evidence of pulmonary tuberculosis was found.

In 1864, Murchison¹⁶ reported a 15-year-old boy, who had anemia and discoloration of the skin for one year. He also had diarrhea, vomiting, and color like a "Negro." Cause of death was erysipelas of the face. Autopsy revealed old pulmonary tuberculosis, tuberculous peritonitis, and large caseous adrenals.

In 1865, Murchison¹⁷ presented a 15-year-old boy, ill more than one year, who had an occasional convulsion, pain in the back, diarrhea, and clinical findings of tuberculous peritonitis, and pigmentation. Autopsy showed tuberculosis of the lungs, peritoneum, and both adrenals.

In 1865, Greenhow¹⁸ described a 13-year-old girl, who had all the classical symptoms and signs of Addison's disease for six months before death. Autopsy revealed generalized tuberculosis involving the mesenteric glands, and lungs, and both adrenal glands were completely destroyed by cheesy material.

In 1866, Rossignol¹⁹ reported a 15-year-old girl with "bronzing" skin, generalized weakness, and anorexia for two months. Both adrenals were enlarged, two inches long, filled with hard, yellow "putty like" material.

In 1866, Parker²⁰ described a 15-year-old girl, with a seven weeks' illness with asthenia, vomiting, weight loss, and "melanoderma." Post-mortem revealed pulmonary tuberculosis and caseous adrenals.

In 1866, Little²¹ presented the case of a 15-year-old girl, who had been delicate "all of her life" but had no definite illness until four weeks before her death. There were symptoms of weakness, vomiting, "fainting attacks," and generalized pigmentation of the skin and mucous membranes. Autopsy findings revealed tuberculosis of the lungs and adrenals.

In 1866, Faure and Barthéz²² described a 14-year-old boy with pigmentation of the skin for one year, intermittent convulsions, weakness, attacks of diarrhea. Autopsy showed "congestion of meninges," supposedly tuberculous meningitis, and tuberculosis of both adrenals.

In 1867, Heckford²³ reported a 14-year-old girl, who had been treated for arthritis in the hospital. Her complexion was "gypsy like," and she had attacks of convulsions, weakness, and somnolence. There was no diagnosis during life. Post-mortem revealed tuberculous degeneration of both adrenals, nothing else.

In 1868, Arnett²⁴ described a boy, 13 years of age, with extensive tuberculosis of the spine and many other bones. There was slight bronzing of the skin. Post-mortem showed amyloid disease of the spleen and lungs, but the bronchial glands were free of disease. Kidneys and left suprarenal gland were normal. The right adrenal was large, nodular, and contained many caseous deposits. There was some ulceration of the intestines and large mesenteric glands. The lungs were clear.

In 1870, Guttman²⁵ presented the case of a girl, aged 11 years, who had been debilitated for a year, and whose death was sudden with gastrointestinal symptoms predominating. There was pigmentation of the skin. At autopsy the right adrenal was found intact, and the left adrenal contained a large, calcified focus.

In 1872, Nicholson²⁶ reported a case of a boy, 14 years old, who had classical signs and symptoms of Addison's disease. Autopsy showed both adrenal glands to be completely destroyed by tuberculous material. There was no evidence of tuberculosis elsewhere.

In 1876, Andrew²⁷ described a 15-year-old boy, with generalized bronzing of the skin, and discolored mucous membranes. There was weakness, intestinal upsets, crepitation at right lung base, pain in the kidneys, and increasing cough. He had had three attacks of rheumatic fever in the past three years. Post-mortem showed the thymus to be enlarged, hemorrhage in the pleural space, and findings of endocarditis. Both adrenals contained a large amount of caseous material.

In 1876, Pye-Smith²⁸ reported a case of a 14-year-old boy with signs and symptoms of Addison's disease. Three hours before death, he screamed with pain and became unconscious. At autopsy there was calcification of the adrenal glands, and tuberculous involvement of the bronchial glands.

In 1877, Carter²⁹ described a boy, aged 14 years, with recurrent attacks of severe headache and vomiting. There was no discoloration of the skin; however, autopsy revealed that both adrenals were completely destroyed by tuberculous lesions and, in addition, there was active tuberculosis of both lungs.

In 1879, Renton³⁰ presented a girl, aged 13 years, who had been debilitated for many months, with gradual weight loss, weakness, and a marked "melanoderma." Necropsy revealed extensive tuberculosis involving numerous abdominal glands, a direct extension of the tuberculous process into the sheath of the solar plexus, and marked degeneration of the adrenal glands and associated sympathetic ganglia.

In 1879, Smith-Shand³¹ briefly described a boy, aged 13 years, whom they saw for the first time in a moribund condition. Marked emaciation and generalized pigmentation of the skin and mucous membranes were reported, and both adrenal glands were said to be in an "abnormal state." The exact nature of the pathologic process was not given. The patient's hair looked as if "it had been washed with a solution of nitrate of silver."

In 1881, Wright³² described a boy who had been ill for three years with symptoms of active pulmonary tuberculosis, but in addition there was definite generalized pigmentation. The patient expired when 8 years of age, and the right adrenal and right kidney were found to be completely destroyed by caseous material. The left adrenal was intact. There was a history of tuberculosis in the family.

In 1882, Franks³³ presented a case of a girl, aged 14 years, who had been ill for two months with typical symptoms of Addison's disease. Both her father and mother were known to have had active pulmonary tuberculosis. At autopsy there was generalized tuberculosis of the mesenteric glands, caseous deposits in both adrenals, and active tuberculosis of the left lung.

In 1883, West³⁴ described the case of a girl, aged 14 years, who had symptoms for two years consisting of marked weakness, loss of weight, abdominal discomfort, and frequent fainting episodes. There was an increased pigmentation of the skin and mucous membranes, and at necropsy there was tuberculous involvement of both adrenal glands and widespread pulmonary tuberculosis.

In 1883, Church³⁵ reported a case of a girl, aged 9½ years, who had a history of intimate exposure to active tuberculosis in the family. For twelve months she exhibited classical signs and symptoms of Addison's disease and expired following a convulsion. The left adrenal was replaced by tuberculous material, and on sectioning the right adrenal a large calcareous body was seen. In addition, there was evidence of old tuberculosis involving the left pulmonary apex.

In 1885, Monti³⁶ described a case of a boy, 10 years of age, who had symptoms over a period of three years suggestive of the diagnosis of chronic adrenal insufficiency. He expired following a period of convulsions and coma. There was marked generalized pigmentation of the skin. The autopsy findings in this case were very unusual in that the right adrenal was completely absent and the left was unusually small and atrophied. There was a mild, generalized hyperplasia of all lymph glands and enlargement of the spleen. The atrophy of the adrenal gland was thought to be due to "chronic interstitial inflammation." There was no evidence of tuberculosis. This is the first case of atrophy of the adrenal reported in a child.

In 1893, Augagneur and Berard³⁷ presented a case of a girl, aged 12 years, with typical symptoms of Addison's disease with pigmentation of the skin. Grafting of adrenal tissue was attempted but this was followed by hyperpyrexia, vomiting, diarrhea, and death within a few hours. In addition to a diffuse tuberculosis of both adrenal glands, there was evidence of tuberculous peritonitis and active pulmonary tuberculosis.

In 1893, Descroizilles³⁸ described a girl, aged 14 years, with typical symptoms and signs of Addison's disease, ending with a severe diarrhea and death, one year later. Tuberculous involvement of both adrenal glands was found, and in addition there was some enlargement of all the glands throughout the body, including the thymus.

In 1895, Schotte and Risel,³⁹ cited by Dezirot, reported a case of a 15-year-old girl, who was ill for approximately a year with anorexia, nausea, and constipation. Autopsy revealed pulmonary tuberculosis, and the adrenal glands were replaced by cartilaginous tuberculous masses.

In 1895, Descroizilles⁴⁰ presented a 14½-year-old girl with asthenia, weight loss, fever, cough and vomiting, and pigmentation, of three months' duration. Her mother had pulmonary tuberculosis. Autopsy revealed pulmonary tuberculosis, large thymus weighing 30 grams, enlarged mesenteric glands, and both adrenals caseous.

In 1895, Anglade and Jacquin⁴¹ described a mentally retarded girl 4 years of age, who developed generalized pigmentation of the skin shortly before death. Both adrenal glands were said to be sclerotic and markedly atrophied. There was generalized atrophy of the brain, especially noticeable in the frontal lobes and there were a few tubercles throughout the cervical cord and lungs.

In 1897, Schilling⁴² reported a case of a boy, aged 13 years, who presented the classical signs and symptoms of Addison's disease with short periods of remissions and exacerbations, and death three years later. Autopsy revealed tuberculous involvement of both adrenal glands, not associated with active tuberculosis elsewhere.

In 1897, Bury⁴³ reported a case of a girl, 13 years of age, who had "mulatto" appearance of the skin for two years and for one year had been bothered with generalized weakness and frequent intestinal upsets. A diagnosis of Addison's disease was made. "The suprarenal capsules from sheep were pounded up in a mortar with glycerine and a teaspoonful of this mixture was given three times a day." A few days later she expired. Post-mortem examination was made, and the adrenals were found to be completely destroyed by a tuberculous process. There were no pathologic changes elsewhere.

In 1898, Legg, Wickham, and Ormerod⁴⁴ described a 15-year-old boy, presenting typical signs and symptoms. He had weakness, anorexia, weight loss, and pigmentation. Autopsy showed tuberculosis of the right lung, mesenteric glands, and both adrenals.

In 1898, Moizard and Bernheim⁴⁵ published a case of an Italian boy, aged 14 years, with typical signs and symptoms of Addison's disease, and death in two months' time. There were findings of generalized miliary tuberculosis in-

volving the lungs, intestines, spleen, liver, and kidneys. Both adrenals were completely destroyed.

In 1899, Lartigau and Happel⁴⁶ presented a case of a 12-year-old boy, who was ill five or six weeks, with a "tired feeling" which gradually increased in severity and was associated with marked vertigo and dyspnea on very slight exertion. There were also recurring gastrointestinal symptoms. The child was very small for his age and had an emaciated appearance, subnormal temperature, and a weak, feeble pulse. The skin was "copper discolored." The pigmentation was especially noticeable over the backs of the hands, forehead, temples, nipples, scrotum, and penis. The patient gradually improved for a period, although pigmentation of the skin became increasingly worse. Death was sudden, following a generalized convulsion. Autopsy revealed diffuse tuberculous involvement of the lung, and caseation of both adrenal glands.

In 1900, Netter⁴⁷ described the case of a 3-year-old girl, who was apparently healthy until three days before death. She had slight but generalized pigmentation of the skin, vomiting, diarrhea, and signs of peritonitis. Both adrenals were found to be tuberculous.

In 1900, Nattan and Larrier⁴⁸ described a case of a boy, aged 13 years, who for seven years had "recurring cold abscesses" and suddenly became ill with extreme exhaustion, vomiting and diarrhea, and bizarre mental reactions which may be interpreted as those associated with hypoglycemia. In addition, there was a generalized pigmentation of the skin. At autopsy both adrenal glands were found to be completely replaced by caseous material.

In 1904, Nobecourt⁴⁹ presented a case of a boy, aged 13 years, with classical signs and symptoms of Addison's disease. Death came suddenly, following a generalized convulsion. There was active pulmonary tuberculosis and a tuberculous process involving the mesenteric glands and both adrenals.

In 1905, Anglade and Jacquin⁵⁰ described a mentally retarded girl, aged 12 years, who presented a gradual downhill course, characterized by periods of vomiting and diarrhea. There was generalized pigmentation of the skin. At autopsy, evidence of military tuberculosis, involving all organs of the body, was found. The normal structure of the adrenal glands was completely replaced by the tuberculous process.

In 1905, Nobecourt and Paisser⁵¹ published a report of a 13-year-old boy who displayed the usual symptoms of Addison's disease with generalized discoloration of the skin. The adrenals and adjacent mesenteric glands were found to be tuberculous.

In 1913, Langmead⁵² presented a case of a boy aged 10 years, living with four relatives, all of whom later died of pulmonary tuberculosis. There was mild generalized pigmentation of the skin of a year's duration and only a moderate degree of weakness. The child suddenly became ill with persistent vomiting and loss of consciousness; he expired within a few hours. Post-mortem examination showed generalized tuberculosis involving both adrenal glands, lungs, and liver. The spleen was enlarged and the heart was very small.

In 1917, Klein and Kux⁵³ described a case of a boy, aged 12 years, with the history of intimate exposure to active tuberculosis in his immediate family. There was a gradual downhill course over a period of a few months, associated with listlessness, mild but generalized pigmentation, and weight loss. Post-mortem revealed generalized tuberculosis, with extensive involvement of both adrenals.

In 1917, Comby⁵⁴ presented a case of a girl, aged 13 years, with the usual symptoms of Addison's disease. The skin showed generalized pigmentation. There was a history of tuberculosis in the family. Autopsy revealed generalized tuberculosis involving the lungs. There was extensive destruction of the right adrenal and right kidney. The left adrenal was also involved, but to a lesser extent.

In 1933, Duff and Bernstein⁵⁵ described what is probably the first case reported in the American literature, of atrophy of the adrenal gland causing Addison's disease. This boy, aged 14 years, expired at Johns Hopkins Hospital, July 29, 1901. He had had three previous admissions to the hospital, had severe measles at 2 years, whooping cough at 5 years, scarlet fever at 7 years. At 8 years, he had chills and fever, which were diagnosed as malaria, and at that time generalized pigmentation of the skin was noticed. The mother stated that the child had had some increase in pigmentation since the age of 6 years. His condition was diagnosed as Addison's disease at 10 years of age. He had always been active and had no intestinal upsets. On his last admission to the hospital in 1901, he had typhoid fever, to which he succumbed within a few days. Dr. E. L. Opie performed the autopsy and gave the anatomical diagnosis, "Addison's disease, and atrophy of the adrenal cortex with lymphocytic infiltration in the cortex and medulla. The spleen, intestinal tract and mesenteric glands were that of typhoid." There was no evidence of active tuberculosis. The adrenals were very small and together weighed only 2.2 grams.

In 1935, Thompson⁵⁶ described a case of a girl, aged 10 years, with typical symptoms and signs of Addison's disease of six months' duration, ending with sudden death following a period of unconsciousness. There was tuberculous involvement of both adrenal glands and all abdominal glands.

In 1935, Snelling and Erb⁵⁷ described a case of a boy, 9½ years of age, presenting the usual signs of marked emaciation, asthenia, pigmentation, and low blood pressure, and sudden death following convulsion. The heart was found to be very small, weighing only 77 grams, and there was a marked atrophy of both adrenal glands, leaving only a few cortical cells in the left gland; no semblance of cortex could be found in the right. The right gland weighed only 1.4 grams and the left gland, 1.6 grams. The cause of this atrophy is not known. There was no evidence of tuberculosis.

In 1936, Friedman⁵⁸ reported a case of a boy, aged 12 years, presenting a downhill course of six months' duration, with tuberculosis of the lungs, generalized weakness, weight loss, low blood pressure, but with no pigmentation of the skin or mucous membranes. Post-mortem examination, however, revealed a definite tuberculous involvement of both adrenal glands in addition to the pulmonary involvement.

In 1939, Butler, Ross, and Talbot⁵⁹ presented a very interesting case of a 20-month-old boy, who had the following signs and symptoms. From the age of 2 weeks, macrogenitosomia, brownish pigmentation of skin, sudden collapse on restriction of fluids, or on removal of added salt in the diet. During periods of collapse the patient would become dehydrated, show lowering of serum sodium and elevation of serum potassium concentrations. Excessive amounts of estrogen and androgen were excreted in the urine. The child was maintained in fairly good nutritional balance by the daily addition of 2 to 3 Gm. of sodium chloride and 1 or 2 Gm. of sodium bicarbonate to the diet. This is the first and youngest reported case of macrogenitosomia associated with typical signs and symptoms of Addison's disease. The patient was alive and doing well, without the use of cortical extracts or desoxycorticosterone. No follow-up has been reported.

In 1939, Renshaw and Manning⁶⁰ presented a case of a boy, aged 12 years, with signs and symptoms suggestive of appendicitis. He had recurring abdominal discomfort over a period of two years, and expired shortly after entering the hospital. The right kidney was found to contain a small tubercle, and both adrenal glands showed marked caseation with little calcification. There was a generalized brownish pigmentation of the skin.

In 1940, Wilkins, Fleischmann and Howard⁶¹ described a case of "macrogenitosomia precox, associated with hyperplasia of the androgenic tissue of

the adrenal and death from cortico-adrenal insufficiency." This was a 3½-year-old boy, who presented precocious development of the sex organs since the early months of life. It was interesting to note that a sibling was a female pseudohermaphrodite. The child showed a mild, but diffusely increased pigmentation of the skin and gums. In Addition, there was a low blood sodium, high nonprotein nitrogen, and a decided craving for salt. The patient died suddenly. The adrenal cortex was largely composed of androgenic tissue, apparently replacing all other elements of the cortex. The testes were also enlarged and composed of "androgenic zone" tissue. As the author states, this is the first case with definite proof that death from adrenal insufficiency resulted from the destruction of the cortex of the adrenals by encroachment of the androgenic zone.

In 1940, Ginandes⁶² described the case of a 12-year-old boy, with a history of exposure to tuberculosis by his father. He developed progressive asthenia, emaciation, and pigmentation of the skin and mucous membranes. The blood pressure was very low, the basal metabolic rate was -33, and the tuberculin test was positive. X-ray showed a very small "drop-type" heart. There was a dramatic response to administration of glucose and sodium chloride solution intravenously. X-rays of the abdomen showed some calcification of the adrenal glands. Blood chemistry revealed low serum sodium and high potassium. The patient was placed on a diet low in potassium, high in sodium and vitamins, but because of several crises, adrenal cortical extract was given daily. The child took this for one year and showed definite improvement. He gained weight and at the end of this time had a normal blood pressure and normal sodium and potassium levels. The author states that desoxycorticosterone acetate will be tried shortly. No follow-up reports were given.

In 1941, Thelander and Cholfin⁶³ presented a very interesting case and should be complimented for making an accurate diagnosis of such a young child. The patient was a boy, birth weight 7 pounds, 10 ounces, requiring resuscitation because the cord was wrapped around the neck three times. The child improved and nursed well three days later. At the age of 8 days, a few loose stools were noticed; this was followed by a weight loss and regurgitation of food. At 11 days of age, the baby became sleepy, was difficult to rouse, and the stools remained loose. The child was given salt and water solution by mouth, a blood transfusion and parenteral fluids. At 3 weeks of age, the weight was 6 pounds, 7 ounces, and a diagnosis of probable adrenal insufficiency was made. At 1 month of age, there was sudden collapse and the following day the blood sugar was 74 mg. per cent and blood chloride 441 mg. per cent. The child was given 0.2 c.c. of per cortin (desoxycorticosterone acetate) by hypodermic injection, and saline was added to the formula. Immediately following this, the patient began to gain weight and was discharged from the hospital with instructions to the mother to continue the injections of cortical extract. The penis was quite large at birth, but at 6 months of age, the enlargement was unmistakable; pubic hair and a low deep voice were noted. At 9 months of age, the child was readmitted to the hospital with exanthem subitum and has since done quite well on desoxycorticosterone in propylene glycol, 3 drops five to six times a day, sublingually.

In 1942, Anderson⁶⁴ wrote a very excellent paper, entitled, *Significance of Adrenal Insufficiency in Childhood*, and reported a case of primary Addison's disease in an 11-year-old boy. This boy manifested all the clinical signs and symptoms characteristic of Addison's disease. The child was well until 10 years of age, when he became listless and an extensive tanning of the skin noted during the summer failed to disappear the following winter. In addition, there was a gradual increase in weakness, frequent episodes of nausea and vomiting,

and a definite craving for salt. Physical examination revealed a deep, generalized pigmentation of the mucous membranes and cheeks. The heart was small, and the testicle was absent on the right. After a fifteen-hour fast, the blood pressure dropped to 62/38, serum chlorides were 355 mg. per cent; sodium, 299 mg. per cent; potassium 28 mg. per cent; and urea nitrogen, 33 mg. per cent. The fasting blood sugar was 89 mg. per cent, and the carbon-dioxide combining power of the blood was 49 volumes per cent. The tuberculin and Wassermann tests were negative. The intravenous pyelograms were nonrevealing. Intravenous glucose with sodium chloride was given in large amounts. Desoxycorticosterone acetate and cortical extract (Upjohn's) were given in large doses, resulting in a lowering of the potassium level and an increase in the sodium level; 5.0 mg. desoxycorticosterone acetate, and 6 c.c. of adrenal cortex were given daily. Following this medication, the child returned to the farm and resumed his normal duties. Medication was eventually changed to 5.0 mg. desoxycorticosterone acetate in propylene glycol, given sublingually two times a day, and the patient was doing very well on this dosage at the time of their report. Since there was no clinical evidence of tuberculosis or tumor, the diagnosis of primary atrophy of the adrenal gland was made.

In 1943, Rosin and Friedman⁵⁵ described a case in a boy, 7 years of age, admitted to the hospital with symptoms of sleeplessness for a period of four days. The parents had noted that the skin was becoming darker in color about two or three months before; this was followed by marked enuresis, weight loss, and excessive fatigue upon minor exertion. A few days before entry, the child started to vomit, became more listless and gradually stuporous. The past history may be significant. There was severe pneumonia at 2 years of age, associated with very high fever of five to six weeks' duration. Between the ages of 5 and 6 years, the child had chickenpox, measles, and whooping cough, each accompanied by very high fever of many weeks' duration. The patient had enuresis "all of his life," but this was much exaggerated the last few months. The early developmental history was negative. The father and mother were living and well, and two siblings aged 9 and 6 years, were in excellent health. Physical examination revealed the patient to be dehydrated and stuporous. There was a generalized brownish pigmentation of the skin and the mucous membranes, the latter presenting a purple-brown color. Wassermann and tuberculin tests were negative. The blood chlorides were 436 mg. per cent; sodium, 320 mg. per cent; and potassium, 32 mg. per cent. The basal metabolic rate was -27 and the glucose tolerance test showed: fasting, 80 mg. per cent; 1 hour, lost; 2 hours, 100 mg. per cent; 3 hours, 103 mg. per cent; 4 hours, 100 mg. per cent; and 5 hours, 69 mg. per cent. X-rays of chest, abdomen, and skull were all negative. A very decided improvement followed the administration of adrenal cortical extract and intravenous glucose and salt solution. When the therapy was discontinued, relapses occurred. One week following therapy, the blood chlorides were 528 mg. per cent; sodium, 314 mg. per cent; potassium, 28 mg. per cent; and nonprotein nitrogen, 33 mg. per cent. The patient was given 5.0 mg. desoxycorticosterone acetate daily, but received this for only three days, because he was moved out of town. No follow-up reports were given. A diagnosis of atrophy was made because of the history of repeated severe infections in early childhood and the failure to prove that the child had any evidence of tuberculosis or adrenal tumor.

In 1946, Jaudon⁵⁶ presented a case of a 3-year-old girl, who suddenly became ill at 4½ months of age, with high fever, cough, and a generalized maculopapular rash. These symptoms disappeared in a few days, but two weeks later she developed anorexia, became listless and intermittently drowsy, began to vomit projectily once or twice a day, developed diarrhea, and lost weight.

Her previously very fair skin was noticed to be darker in color. She entered the hospital at 6½ months of age, was markedly dehydrated, and chronically ill; there was a faint generalized "tan-like" discoloration of the skin. The serum carbon dioxide combining power was 42 volumes per cent and nonprotein nitrogen, 80.5 mg. per cent. Parenteral therapy was followed by such a dramatic improvement that the patient was almost discharged. However, after twenty-four hours had elapsed without subcutaneous or intravenous fluids, she again refused food, became listless and dehydrated. The Wassermann was negative. An intradermal tuberculin test was markedly positive, almost to the point of ulceration. It was discovered that the Negro house-man had a diffuse "honeycomb" destruction of the left lung, caused by active tuberculosis from which he later expired. The possibility of Addison's disease was considered and 2.0 mg. desoxycorticosterone acetate were injected daily. Two days later, the serum chlorides were 520 mg. per cent; sodium, 300 mg. per cent; potassium, 28.6 mg. per cent; nonprotein nitrogen, 64 mg. per cent; and serum carbon dioxide combining power, 49 volumes per cent. Twenty days later the patient appeared normal in every respect, and the skin was slightly less pigmented. At this time the nonprotein nitrogen was 40.5 mg. per cent; serum chloride, 630 mg. per cent; sodium, 332 mg. per cent; and potassium, 21.1 mg. per cent. The fasting and post-prandial blood sugar determinations ranged between 20 to 50 mg. per cent but were not accompanied by symptoms of hypoglycemia. After a few days on desoxycorticosterone acetate, the appetite improved remarkably and the blood sugar level returned to normal. Pyelogram and urine examinations were essentially negative. The patient was given a high vitamin low potassium diet, and 2.0 Gm. of additional sodium chloride and 1.5 to 2.0 Gm. desoxycorticosterone acetate daily. The case has been followed for over two years. The growth and development have been normal and general health has been excellent. There has been a progressive increase in pigmentation of the skin and mucous membranes to almost "Negro" black over the exposed surfaces. Omitting the extract for twenty-four hours resulted in an immediate decrease in appetite and weight. No symptoms of hypoglycemia have developed. There was no real evidence of a tuberculous infection of other than the adrenals to account for the markedly positive tuberculin reaction. It was thought that this test was sufficiently significant in an infant 6 months of age to make the possibility of tuberculous destruction of the adrenals likely. The absence of abnormal sexual development and the failure to find an adrenal tumor supported this diagnosis. The possibility of a nontuberculous atrophy of the adrenals, associated with a tuberculous infection in some other part of the body, has not been entirely ruled out.

The following is a summary of the cases classified as *probable*:

Atkinson⁶⁷ mentioned that the first case in a child was published by Hutchinson and Startin in 1855.⁶⁸ This was a boy, aged 12 years, who had symptoms and signs of Addison's disease for a period of four months prior to death. About one year previously, he developed multiple abscesses of the jaw, back, and neck, and had a hacking cough from which he had not completely recovered when the skin pigmentation was first noted. There was "copper Indian" color of the skin. There was no autopsy.

In 1874, Caslodi⁶⁹ described a 15-year-old girl, ill for one year with asthenia, digestive upsets, and pigmentation of the skin and mucous membranes. She showed improvement but was lost sight of.

In 1886, Belaieff⁷⁰ was one of the first to oppose the prevalent view that Addison's disease was caused exclusively by tuberculosis of the suprarenal capsules. He presented the following case which had been quoted by Atkinson as the youngest child reported with Addison's disease. "A male child, apparently

7 days old, was found in the street. The integuments were slightly yellowish, with a gray tint. Later, the yellowish discolorations disappeared, and the skin gradually assumed a dirty gray color, most intense on the back and belly, and especially about the navel. Notwithstanding a good appetite, the child gradually became very weak and emaciated and died 53 days after admission to the hospital, having become unconscious during a paroxysm of tonic and clonic convulsions." There was no fever. The autopsy showed that both suprarenal capsules were considerably enlarged, measuring 1 inch by $\frac{3}{4}$ inch, their upper two-thirds being transformed into an aggregate of thin-walled, semi-transparent cysts, varying in size from a pinhead to a small cherry. Their content was a clear, serous fluid.

In 1889, Pottier⁷¹ presented an 11-year-old girl having typical signs and symptoms of Addison's disease. This child eventually expired, but no autopsy was performed.

In 1894, Goulon⁷² described the case of a 6-year-old girl with active rheumatic fever and chorea. While under treatment, she developed anorexia, marked fatigue, and generalized "bronzing" of the skin. The patient was lost sight of.

In 1897, Comby⁷³ described a case of a boy, aged 14 years. He had an illness of a few days' duration with signs and symptoms suggestive of Addison's disease, including generalized pigmentation. The distribution of this pigmentation, which gradually increased in severity, was highly suggestive of this disease. Comby reported definite improvement with the use of sheep's adrenal gland extract, but unfortunately the patient was lost sight of.

In 1897, Variot⁷⁴ reported a case in a girl, aged 14 years, with signs quite characteristic of Addison's disease. Injections of an adrenal extract were given for a time and the intestinal symptoms disappeared and the pigmentation definitely diminished. This case was not followed.

In 1898, Variot⁷⁵ (quoted by Dezirot) described a 14-year-old boy with weakness, "chocolate" discoloration of the skin, and poor muscular strength. Improvement was noted when sheep's adrenal gland was given orally. The patient was lost sight of.

In 1899, Maisch⁷⁶ presented a case of a 12-year-old boy, with all the classical signs and symptoms of Addison's disease, without clinical evidence of tuberculosis. Unfortunately, this patient was lost sight of. Maisch also described two male infants, 9 and 7 months of age, with generalized pigmentation of the skin, who presented alternating periods of diarrhea and constipation resulting in asthenia and death. Post-mortem examination failed to reveal anything abnormal in the adrenals.

In 1900, Fleming and Miller⁷⁷ reported what appeared to be Addison's disease in a 28-year-old mother and her four children. The mother had signs and symptoms, suggestive of Addison's disease, which dated from her first pregnancy seven years previously and gradually progressed. The first child, a girl aged 7 years, had had excessive pigmentation for four years, associated with headaches, stomach ache, and diarrhea. The second girl, aged 4 years, developed dark skin one year before, following an attack of eczema. She was also subject to diarrhea and vomiting. Their brother, aged 3 years, had always been a dark-skinned child. There were dark spots scattered all over his body, which had begun to appear only six months before. This boy, too, had gastrointestinal disturbances of an unexplained nature. The youngest child was a girl, 2 years of age, who had previously been of very fair complexion. But she had become distinctly darker over a period of four to five months. Diarrhea was occasionally noted. Unfortunately, there has been no follow-up of these cases. They were all living at the time of the report.

In 1907, Felderbaum and Fruchthandler⁷⁸ described a girl, 12 years of age, whose maternal grandmother and mother had died of tuberculosis. The child

had a generalized pigmentation of the skin and other symptoms quite suggestive of Addison's disease. The patient was chronically ill for a number of months and expired following a convulsion lasting eight hours. It was stated that the intestinal contents "contained large number of oval egg bodies." No autopsy was performed.

In 1907, Chemin⁷⁹ reported a case of a girl, aged 13 years, who for a year previously had been gradually going downhill with recurrent bouts of diarrhea and abdominal pain associated with a generalized pigmentation of the skin. The child had a moderate, secondary anemia. She was given an extract of adrenal gland daily, resulting in definite improvement. The author stated that the child was alive, but there has been no follow-up since that time.

In 1912, Gallais⁸⁰ reported an adenogenital syndrome in a girl who showed definite evidence of muscular weakness and generalized pigmentation. Therapy was not instituted and no follow-up reports have appeared.

In 1920, Orel⁸¹ described a child, a brother of the patient presented by von Priesel.⁸² This patient had typical macrogenitosomia and symptoms suggestive of chronic adrenal insufficiency, including the typical pigmentation. The child suddenly expired following a generalized convulsion. Unfortunately, no autopsy was obtained.

In 1921, Figenschau and Berner⁸³ reported a 4½-year-old girl who had been chronically ill with marked malnutrition and asthenia, had generalized pigmentation, and died suddenly following a period of coma. The left adrenal gland was completely occupied by a neuroganglioma. The right adrenal gland was apparently normal.

In 1932, Rossi⁸⁴ gave a detailed description of the symptomatology of this disease in children. He presented a case of a boy, aged 6 months, whose natural father was actually the grandfather of the child. The patient was full-term and apparently normal until 6 months of age, when an arrest in growth was noticed. Following this there were symptoms of diarrhea, weight loss, loss of vivacity, and the gradual appearance of a dehydrated and bronze-colored skin. These symptoms finally terminated in marked asthenia, fever, and continuous somnolence. Physical examination revealed marked rickets and a brownish tinge of the eyelids, neck, axillary region, backs of hands, feet, and around the genitalia. There was no evidence of sexual precocity and the cutaneous tuberculin reaction was negative. His death at 11 months of age, was preceded by sudden high fever, cough, and dyspnea. The post-mortem findings revealed bronchial pneumonia at the bases of both lungs, fatty degeneration of the myocardium, slight enlargement of the liver and spleen, and complete absence of the right kidney, corresponding ureter and renal vessels. There was enlargement of the left kidney and increase in its consistency, and the cut surface showed a grayish color. The adrenal gland on the right was in normal position, somewhat reduced in size and the consistency increased. Histologic examination showed nothing particularly abnormal in regard to the cortex, but the medullary tissue was completely absent over a large portion of the gland, and in its place there was only a scarce chromaffin cell. The left adrenal gland was in the normal location and histologic alterations were similar to that noted. The author states that the age, history, and absence of any signs of an inflammatory process, point to this being a congenital lesion.

In 1936, Namiki and Nitto⁸⁵ reported a 10-month-old girl with signs and symptoms suggestive of Addison's disease. Death was sudden, but no autopsy was performed.

In 1936, Harnapp⁸⁶ presented a boy, aged 12 years, with pigmentation of the skin of three years' duration. Complaints of intestinal upsets and headaches were noted. The patient responded to treatment with cortical extracts,

common salt, and ascorbic acid. Exacerbations of these symptoms continued despite therapy. The serum chlorides ranged from 364 to 387 mg. per cent; the sodium, 238 to 260 mg. per cent; and potassium, from 17.7 to 18.8 mg. per cent. Dextrose, galactose, fructose, and adrenalin tolerances were done. The tuberculin and Wassermann tests were negative. The child was alive at the time of presentation, but there have been no follow-up reports.

In 1936, Kagan and Høleberg⁸⁷ described a case of a boy, 11 years of age, who entered the hospital in a state of collapse, responding promptly to the administration of salt solution in large doses. The child suddenly became worse when discharged from the hospital but again improved when 6.0 Gm. of sodium chloride were put in his milk daily. There were no reports on the blood chemistry, adrenal extract was not used, and there has been no follow-up.

In 1937, Borghini⁸⁸ presented a 13-year-old Italian boy who had been delicate all of his life. He was a thin, undernourished boy, subject to attacks of weakness upon slight effort. The skin was uniformly pigmented. His mother died of typical Addison's disease; however, this pigment was followed for five years with no noteworthy change in his condition. No statement was made as to therapy and there have been no follow-up reports.

In 1940, Casaubon and Cossoy⁸⁹ described a 12-year-old girl whose skin became pigmented, and who presented symptoms of one year's duration suggestive of Addison's disease. The tuberculin and Wassermann tests were negative. The serum sodium was 335 mg. per cent. Despite the administration of cortical extract and adrenalin, the patient had a generalized convulsion and expired. No autopsy was performed.

The following cases are thought not to be Addison's disease, and are classified as *doubtful*:

In 1863, Steffen⁹⁰ presented a 7-day-old girl, without signs or symptoms of Addison's disease. The patient expired two months after an operation for harelip. At autopsy very large hemorrhagic adrenals were found.

In 1865, Pitman⁹¹ described a 3-year-old girl as a case of Addison's disease. There was generalized hirsutism with no increased pigmentation of the skin. The child expired following an attack of continuous vomiting. The right adrenal was normal, but the left was destroyed and replaced by a very large medullary cancer, weighing 2 pounds, 5 ounces. The liver was also cancerous.

In 1866, Faure⁹² described a case of a 13-year-old boy with extensive tuberculosis involving the vertebrae and causing much destruction of other bones. The patient did present symptoms of Addison's disease, but there was no generalized pigmentation of the skin. At autopsy the left adrenal gland was found to be normal and the right adrenal was enlarged, containing a few miliary tubercles. The lungs, mesenteric glands, and intestines were normal. However, there was extensive tuberculosis involving the bones. Presence of one normal adrenal gland, only slight involvement of the other, and extensive tuberculosis elsewhere make it seem unlikely that the symptoms of this patient were due to chronic adrenal insufficiency.

In 1879, Goodhardt⁹³ described the case of a 5-year-old child who suddenly expired. There were no symptoms or clinical findings suggestive of Addison's disease. No detailed history or report of the physical findings was given. At post-mortem, tubercles were found in the cerebellum and pons, and one tubercle in one adrenal gland.

In 1895, Zinnis⁹⁴ presented the history of a 3-year-old boy with chronic diarrhea, anemia, and bronzed skin. The child supposedly recovered after treatment with iron and a proper diet.

In 1899, Maisch⁹⁵ reported a 9-month-old boy who presented generalized pigmentation, periods of constipation, diarrhea, and weight loss. At autopsy

there was a generalized increase in melanin pigment in all the viscera without any pathologic evidence to account for the patient's death. The adrenals were said to have been normal.

In 1903, Richon⁹⁵ published a case of a 10-year-old girl, whose father died of pulmonary tuberculosis. She became very weak, lost her appetite. The mother stated her skin had always been dark, but it became more marked on the face, trunk, and groin during the last few weeks. The patient improved with injections of adrenal extract. But three months after the onset of treatment she expired, following an episode of abdominal pain, vomiting, and diarrhea. Post-mortem revealed pulmonary and intestinal tuberculosis but the adrenals were healthy in appearance.

In 1905, Nobecourt⁹⁶ described a case of an 18-month-old boy whose mother had active pulmonary tuberculosis. The child was found to be emaciated, with generalized pigmentation of the skin and mucous membranes. He also presented signs of tuberculous meningitis immediately before death. At autopsy there was evidence of generalized tuberculosis, involving the mediastinal and mesenteric glands, lungs, and spleen. However, the adrenals were normal.

In 1916, Rutelli⁹⁷ presented a 10-year-old boy, who had "brown" skin for six years and a tubercle on one finger. After adrenal extracts were taken, the blood pressure rose from 65 to 82 mm. There was very slight asthenia and no weight loss. No other details were reported.

In 1917, Hertz, Secher, and Pittman⁹⁸ reported the progress of a male patient from 2 to 16 months of age. The child had marked secondary anemia and symptoms of Addison's disease, but no mention is made of pigmentation. At autopsy there was a neuroblastoma of the left adrenal, but the right adrenal gland was normal. The author mentions this case as proof that Addison's disease can occur without the presence of tuberculosis. There were no blood chemistry changes reported.

In 1922, Cannata⁹⁹ described a case of a 16-month-old boy who had symptoms and signs of Addison's disease, including pigmentation. There was spontaneous improvement and there have been no further reports.

In 1927, Morabito¹⁰⁰ presented cases of a brother and sister 7 and 10 years of age, respectively. Each had signs suggestive of Addison's disease. The Wassermann tests were positive. No further details were given. There have been no follow-up reports. It is interesting to note, however, that rare cases thought to have been due to syphilis, have been reported in adults. With institution of antisyphilitic therapy these have improved promptly.

In 1927, Peutz¹⁰¹ published a case of a 12-year-old boy who was doing poorly because of generalized weakness, weight loss, and a secondary anemia. Two members of the boy's immediate family died of tuberculosis. This child, however, was doing well at the time of publication and there has been no further report.

In 1931, Von Priesel⁸² presented a case of a 5-year-old girl with pseudohermaphroditism, secondary to adrenal hyperplasia. He noted that there was generalized pigmentation of the skin, but no other symptoms and signs of Addison's disease. There was no follow-up.

DISCUSSION

In addition to destruction of the adrenals by tuberculosis, neoplasms, and atrophy, the recent literature^{59, 61, 63} has demonstrated that hypofunction of the adrenal cortex, resulting in symptoms of Addison's disease, may be secondary to hyperplasia of the androgenic zone.

In 1940, Dijkhuizen and Behr¹⁰² described a 2-week-old male infant with pseudohermaphroditism, who became ill following vomiting, dehydration, and diarrhea. A diagnosis of intestinal obstruction was made, but operation failed

to reveal the cause. No autopsy was obtained. Later, the brother of this child was hospitalized at 2 months of age, because of episodes of violent vomiting and diarrhea. A diagnosis of intestinal obstruction was again considered. Autopsy showed both adrenals to be very large, presenting marked gyrations and grooves. Together they weighed 22.0 grams.

Through the courtesy of Professor Pelanze of Amsterdam, these authors¹⁰ presented the third case, a boy, who began to vomit and had loose stools shortly after birth. Post-mortem revealed a large thymus and very large adrenals, weighing 12.0 grams each, the same size as the kidneys.

Their fourth case, a 5-week-old girl, had been vomiting constantly for ten days, had diarrhea for five days, became markedly emaciated, and expired at 3½ months of age. Autopsy revealed only very large hyperplastic adrenals, together weighing 34.0 grams.

Even though Dijkhuizen and Behr's four cases were reported as deaths secondary to hyperfunction of the adrenal cortex, it was thought that they more probably represented instances of severe cortical insufficiency, caused by marked hyperplasia of the androgenic zone. Unfortunately, no notation was made about the color of the skin. No chemical determinations were made of the blood, nor was a definite statement made about the genitals, except in the one case of a pseudohermaphrodite. The sizes of the prostates and testes were not recorded.

The case of Wilkins, Fleischmann, and Howard¹¹ unquestionably demonstrated that the androgenic tissue could become so hyperplastic as to cause destruction of practically all of the normal cortical tissue.

Grollman¹⁰³ states: "The symptoms of Addison's disease associated with adrenal virilism are caused by the encroachment of the androgenic zone on the true cortical tissue." If the male patients described by Dijkhuizen and Behr did not show enlarged genitals before death, they might have shown these signs had they lived longer. Wilkins' patient did not show enlargement of the penis until past 3 months of age.

Dijkhuizen and Behr¹⁰² also reviewed the literature and found six additional cases in patients varying from 5 weeks to 3½ months of age. Two of these were pseudohermaphrodites. One newborn female in addition to hyperplasia of the adrenals had a uterus the size of a 5-year-old girl, but the ovaries were normal. All of these patients expired following intestinal upsets. No further details were given.

Even at the present time, it is difficult to differentiate accurately between the hyperplastic androgenic fetal zone and the true cortex, nevertheless there is sufficient similarity between these and the so-called *proved* cases to warrant their classification as *probable*. These cases have not been included, however, since they were not reported as adrenal insufficiency or Addison's disease.

A great deal of consideration was given the case presented by Beliaeff,⁷⁰ since this 7-day-old infant was quoted by Atkinson⁶⁷ as the youngest child reported with Addison's disease. The terminal symptoms, generalized convulsions, and the presence of numerous cysts comprising the upper two-thirds of the adrenals suggested cortical insufficiency as the cause of death. The fact that no histologic evidence of absent or decreased cortical tissue or other post-mortem findings was given, and the absence of true bronzing of the skin, prompted the classification of this case as *probable*.

The cases of Hertz, Secher, and Pittman,⁹⁸ with destruction of one adrenal gland by tumors were classified doubtful because of the absence of pigmentation and the finding of one normal adrenal. There were three proved cases of unilateral tuberculous involvement of the adrenals; however, all these cases, in addition to presenting typical symptoms, also showed generalized pigmentation.

The third case, presented by Figenschau and Berner,⁸³ of complete destruction of one adrenal gland by a neuroganglioma was placed in the *probable* category because of the classical symptoms and pigmentation.

Blood chemical changes and the response to potent extracts are probably the most reliable criteria for use in properly classifying this type of case.

It is felt that reasons for the classification of the other cases require no further explanation.

SUMMARY

One hundred cases of children, below the age of 15 years, have been reported in the literature before June, 1945, with the diagnosis of Addison's disease.

Sixty-two have been classified as *proved*, twenty-three as *probable*, and fifteen as *doubtful*.

The following summary has been made of the *proved* cases:

Age Incidence.—The onset of symptoms was first noticed in children:

Under 2 yr. of age in three, or 4.9 per cent

From 2 to 5 yr. of age in three, or 4.9 per cent

From 5 to 10 yr. of age in seven, or 11.5 per cent

From 10 to 15 yr. of age in forty-eight, or 78.7 per cent

The age was not reported in one case

Sex and Race Incidence.—Thirty-eight, or 61.3 per cent, were males and twenty-four or 38.6 per cent were females, giving an almost 2 to 1 incidence in favor of the males. This ratio is in agreement with that usually quoted in adults with tuberculosis of the adrenals. It is frequently stated, however, that the ratio is reversed in primary atrophy in adult patients. It is, therefore, of interest to note that the children with atrophy of the adrenals were all males. To my knowledge, no cases have been reported in the Negro race.

Symptoms and Signs.—Fifty-three, or 85.5 per cent, of the cases manifested gastrointestinal symptoms some time during the course of the illness. No statement was made concerning the presence or absence of intestinal complaints in the remaining nine, or 14.5 per cent. The incidence of gastrointestinal symptoms, therefore, is probably much higher than that stated. Attacks of vomiting, diarrhea, and generalized abdominal discomfort were the most common complaints. Asthenia, anorexia, weight loss, dehydration, and general debility were present in practically all of the cases. In eight, or 12.9 per cent, there were repeated convulsions which might be interpreted as hypoglycemic in origin.

A definite statement was made concerning the color of the skin in sixty patients. Of these, fifty-six, or 93.3 per cent, had a generalized pigmentation.

The duration of symptoms before death ranged from three days to four years. No definite statement was made in seventeen, or 27.4 per cent, of the cases. Of the remaining forty-five, in twenty-five, or 55.6 per cent, death occurred seven months or less after the onset of symptoms. Twenty, or 44.4 per cent, of the patients were ill for one year or longer.

Mode of Termination.—By far the majority of these children presented the picture of a progressive debilitating illness, resulting in the usual slow death. However, twenty, or 32.2 per cent, of them exhibited dramatic episodes of convulsions, profuse diarrhea or vomiting, or sudden coma just prior to death.

Etiology.—In one case the nature of the pathologic involvement of the adrenals was not given. Of the remaining sixty-one, fifty-three, or 86.9 per cent, were of tuberculous origin, fifty, or 94.3 per cent, showed bilateral involvement of the adrenals. Pulmonary tuberculosis was present in twenty-three, or 43.4 per cent, and tuberculosis of the mesenteric glands was present in seven,

or 15.0 per cent, of the cases showing tuberculous adrenals. In five, or 8.0 per cent, of the cases there was atrophy of both adrenal glands without clinical or pathologic evidence of tuberculosis. In three, or 4.8 per cent, macrogenitosomia was an associated finding. Of the six cases, in which the patients were alive at the time of the report, two were diagnosed atrophy; two, hyperplasia; and two, tuberculosis of the adrenals.

In adults, pyogenic abscesses, vascular lesions, amyloid degeneration, mycosis fungoides and echinococcus cysts have been responsible for destruction of the adrenal glands resulting in the development of Addison's disease. To my knowledge, these etiologic agents have not been responsible for this disease in children.

Treatment.—Although in the older literature there was an occasional reference to the use of crude adrenal extracts, it was not until 1927 that Hartman and associates¹⁰⁴ demonstrated that Interrenalin prolonged the lives of adrenalectomized dogs. The period between 1936 and 1941¹⁰⁵⁻¹¹⁰ produced important contributions in the isolation of various fractions of the whole gland which put potent extracts at the disposal of the clinician. For these reasons, and the lack of knowledge until 1932⁴ concerning the importance of electrolyte metabolism, these patients could not have received adequate therapy until after this time.

In Butler, Ross, and Talbot's case,⁵⁹ associated with macrogenitosomia, there was sudden collapse on restriction of fluids or sodium chloride but the patient was apparently well-regulated on the addition of 2 to 3 Gm. of sodium chloride to the diet, without the use of extracts.

Ginandes' patient,⁶² although probably having tuberculous adrenals, was well-adjusted on daily injections of whole cortical extract. In addition, a diet high in sodium-chloride and low in potassium was prescribed. During the acute phase of the illness a dramatic response was obtained with normal saline and glucose intravenously.

In the other case associated with macrogenitosomia the patient was regulated by substituting physiologic sodium chloride solution for water in the formula and the addition of 0.2 c.c. desoxycorticosterone acetate by injection daily. At 9 months of age the therapy was changed to 3 drops of desoxycorticosterone in propylene glycol, five to six times daily sublingually.

Anderson's⁶⁴ 11-year-old patient with probable atrophy of the adrenals was given 5.0 mg. desoxycorticosterone acetate and 6.0 c.c. whole gland extract daily, by injection. The therapy was later changed to 5.0 mg. desoxycorticosterone in propylene glycol twice daily sublingually.

Rosin and Friedman's patient,⁶⁵ a case of adrenal atrophy, was improving on injections of desoxycorticosterone, but he was lost sight of.

Jaudon's patient,⁶⁶ a probable case of tuberculosis of the adrenals, has been well controlled for over two years by injections of 1.5 to 2.0 mg. desoxycorticosterone acetate daily. Recently, four 125 mg. desoxycorticosterone acetate pellets were implanted and daily injections are no longer necessary. The child has remained in good health.

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The Academy Study of Child Health Services

REPORT ON ACADEMY STUDY

Under title of *The Social Aspects of Medicine* in the March issue of the JOURNAL, Dr. Park has thrown an aura of suspicion over the true parentage of the Academy's war baby—now more respectfully known as "The Study of Child Health Services." Partly in order to forestall the appointment of "another committee to investigate," although there is nothing to hide, those of us concerned with rearing this child wish to clarify for Dr. Park and his readers "this mysterious affair." More particularly, however, we are eager to describe the extent to which many friends of the Academy have supported this infant prodigy and have once more demonstrated their faith in the activities of the Academy.

Relationship of the United States Public Health Service and Children's Bureau.—It is apparent that there still exists considerable doubt and misgiving arising from the fact that the United States Public Health Service and the Children's Bureau have been asked to assist in the organization and conduct of this Study. This action was taken in accordance with a recommendation presented to the Academy membership at its annual meeting in November, 1944: "That the American Academy of Pediatrics requests the United States Public Health Service and Children's Bureau to undertake with the Academy a survey in every state to determine . . . information concerning the present situation and extension of personnel and facilities needed in each state to meet the objectives as stated." Those who wish to refer to the full report will find it published in the JOURNAL (J. Pediat. 25: 625, December, 1944). This recommendation having been unanimously approved in open meeting, it naturally followed that Dr. Parran and Dr. Martha Eliot were asked to cooperate with the Academy in this Study. Both responded with wholehearted support, contributing the full-time services of expert medical and statistical personnel and equipment. Cooperative planning was begun and at the same time it was made clear that the control of the project was to remain in the hands of the Academy. Thus there has been established an effective and happy working relationship wherein the authority of the Academy has at no time been questioned.

In view of the desirability of working in close proximity to the two cooperating government agencies, a Central Office was set up in Washington to serve as headquarters for the Director and Executive Staff. Washington was chosen for the Central Office with some hesitation since this location might be interpreted by some as indicating that the Study is a government project. It very definitely is not a government project. The Director is paid by and answerable to the Academy of Pediatrics; the personnel who are on loan from the government agencies are under his direction. The responsibility for the success of the undertaking belongs to the Academy.

Instead of viewing with suspicion and misgiving the intentions of those who recommended this cooperation they should be commended for a step without which the Academy would now find itself in an embarrassing plight. It is fair to state that these planners wrought better than they knew. No one at the outset appreciated the enormous mass of statistical data to be collected or the labor involved in adequate analyses. The Academy does not have at its disposal the necessary statistical facilities or in fact the personnel or experience to undertake a task of such broad scope. Even we at the Central Office appreciate that we do not yet fully visualize all that is involved in drawing together, coding, and tabulating information from all hospitals, medical schools, health services, and physicians throughout the country.

Questions have also been raised with regard to who is to interpret the information and the purpose to which the results of the Study will be put. The function of the Study as it is now organized is to obtain factual material. Much confusion will be avoided if it is kept clearly in mind that this Study is to be considered only as the first step toward the attainment of the Academy's objective which, briefly stated, is to make available throughout the country improved and more evenly distributed medical care for children. At the close of the Study the material will be presented in a report which will be available to all who care to use it. This report will be limited to a presentation of factual data and will not include broad interpretations or recommendations. A program of action resulting from this report will be a responsibility of the Academy at a later date. Only after the facts are known can a fair estimate be made of the interpretations and opinions that may arise from them. In addition to publishing an over-all report, information gathered through the State Programs now under way will be returned to State chairmen of the Academy in tabular form broken down to State, County, or Metropolitan levels. It is hoped thereby to stimulate local groups to evaluate the services within their own communities as a basis for local planning.

The responsibility for collecting and reporting the desired information and also the relationship between the American Academy of Pediatrics, the United States Public Health Service and the Children's Bureau have been repeatedly described at many meetings of the Academy. However, there are many who have been unable to attend these meetings and have not had the opportunity to become fully informed, of whom some still seem to be suspicious of the motives of the government agencies, particularly the Children's Bureau. So again in order to allay any lingering misgivings it is worth reiterating that there is no intention on the part of anyone to use this Study for any dire motive. If, after the facts are gathered and the Academy has drawn up a program based upon them, there are those who wish to oppose that program—and it is hard to believe that such will not be the case—then pediatricians themselves will be able to support their cause by a background of factual data which is now lacking.

National Foundation for Infantile Paralysis.—When the Study was first undertaken not only was its scope underestimated but also its cost. At the outset the Academy appropriated \$8,000 from its reserve fund. More recently it has added another \$10,000 to its appropriation which altogether represents a large proportion of its total reserve fund. This is clear evidence of the earnestness with which the Academy is meeting its own commitment. But even so this is a relatively small proportion of the total expense. It was apparent that grants of major proportions would be needed to help the Academy in this project.

The National Foundation for Infantile Paralysis was one of the first sources to which the Academy looked for help. This Foundation is particularly concerned with improving the resources for one aspect of pediatric care and showed immediate interest in the Academy's Study. After a detailed examination of the proposed plan the Foundation has made a grant of \$116,000 for a two-year period. It is intended that this grant should cover the expenses involved in maintaining the large staff for which the Academy is responsible in the Central Office, salaries and expenses of Regional Directors, cost of preparing and printing questionnaire schedules and publicity material, and general operating expenses of the Central Office. This grant, although generous, is not expected to take care of the cost of State programs throughout the country. However, at the State level the National Foundation for Infantile Paralysis has again come to our support. A memorandum has been sent from the National Headquarters of the Foundation to all their field representatives urging them to encourage County Chapters to give not only moral support but also financial assistance to State programs when asked to do so by the State Chairmen of the Academy. Whether or not financial support is obtained at the State level from the National Foundation it is considered desirable from the point of view of the mutual interests of the Foundation and the Academy that their field representatives and other persons interested in the

County Chapter activities should cooperate in accepting appointments to the Academy State Advisory Committees. The Central Office of the Study has already received word from many States demonstrating the willingness of the Foundation to offer generous support to State chairmen.

Further Financial Support.—In order to stand on as broad a basis as possible in financing this major effort, the Academy has sought support from several of the larger Foundations and also from several of the commercial firms which have special pediatric interest. The Kellogg Foundation has expressed its approval of the Study and has offered to appoint one or more of its trained field workers to assist in the collection of data. A letter has recently been received from the Executive Vice-President of the Field Foundation stating that the Directors of this Foundation have voted a contribution, the amount of which has not yet been specified. The services of the Executive Director of the New York State Study have been contributed by the Metropolitan Life Insurance Company.

Generous support has been received from Mead Johnson and Company, M and R Dietetic Laboratories, Carnation Company, the Pet Milk Company. Lederle Laboratories, Inc., has also stated that they would make a contribution which has not yet been received.

In addition to these grants received by the Central Office, State Chairmen who are responsible for financing State Programs from within each State have received financial contributions from many different sources. So far it appears evident that they have been able to do so without undue difficulty. Support at the State level from the National Foundation for Infantile Paralysis has already been described. In many cases the State Health Department has met part or all of the expenses of the State program by funds available under Title V of the Social Security Act. A few States have sought and received grants from local Foundations. In certain areas contributions have been requested of the pediatricians themselves.

The American Academy of Pediatrics is indeed fortunate in the number of friends who may always be counted upon to come forward and assist its activities. The happy relationships which this Study is promoting throughout the country are well demonstrated by the following quotation from a recent letter of Dr. Theodore E. Allen, Executive Secretary for the Metropolitan New York area: "The response to our never ending letters asking for sponsorship for this Study has continued to be a very happy one. It is a pleasure to open the mail in the morning and see in how many different ways agencies and individuals can say they are pleased to help our project."

JOHN P. HUBBARD, M.D.

The Social Aspects of Medicine

THE BRITISH HEALTH BILL

3rd April, 1946

Dear Dr. Park,

You asked me to secure some views on our new Health Bill, especially if I could persuade people completely opposed and completely in favour to state their case, with a summing up of the moderate view. But it is first necessary to make it clear that with certain few exceptions the medical profession is all "moderate." What I mean is that for a quarter of a century we have all been urging a complete health service and most of what is really good in the present proposals has come from the profession. So that in principle we welcome the bill, although there are many points of detail that require careful consideration and above all we all want to see professional freedom left entirely unfettered. Moreover, the present proposals seem to us to concede much that we have asked for since the original "White Paper" on "A Comprehensive Health Service" was issued by the Coalition Government in February, 1944. There may be—and we hope there will be—still more conceded in the course of the bill's passage through Parliament, and therefore what I am writing may to some extent be out of date before these lines appear. Another important point is that many matters of detail are left to be dealt with in Regulations and in this respect there is as yet no clear picture, for example, of a Child Health Service, on a national scale. But the bill will go through, and root and branch opposition will get us nowhere. The Government has a huge majority. What we must fight for is to get what we think are improvements.

First I will try and summarize very briefly what the bill intends to do. Clause I of the printed bill states the whole issue clearly:

"It shall be the duty of the Minister of Health to promote the establishment in England and Wales* of a comprehensive health service designed to secure improvement in the physical and mental health of the people of England and Wales and the prevention, diagnosis and treatment of illness, and for that purpose to provide or secure the effective provision of services in accordance with the following provisions of this Act. The services so provided shall be free of charge, except where any provision of this Act expressly provides for the making and recovery of charges."

Broadly the provisions proposed fall into three groups. First comes the hospital and special service. The Minister is to take over all hospitals (including mental hospitals)—voluntarily supported or run by local authorities (county councils and borough councils) out of rates. The "Teaching Hospitals" are excepted from this transfer of ownership; that is, those with undergraduates and in some limited instances post-graduate medical schools, although they will have reconstituted governing bodies and have to come into the general plan for hospital services. All such services are to be administered by Regional Hospital Boards, probably about 16 to 20, based upon a university area and with provision for membership by university representatives, the medical profession, the local health authorities of the area and others concerned. These boards will delegate the running of the hospitals to local Hospital Management Committees with small house committees for individual hospitals if required. Specialists will work, so to speak, at and from the hospitals, but no details are available on how they will work, especially as regards domiciliary consultations. It is provided that the Regional Boards shall be given as much financial freedom as possible, by a system of block annual budgets or otherwise.

Next comes the provision of Health Centres and all general practitioner services. The Centres will be provided and equipped by the local authorities (county and borough councils),

*Scotland will be dealt with in a separate bill.

but the doctors will work under a new body—the Local Executive Councils with half membership for local practitioners and half from the major local authorities of the area concerned. Doctors will be paid a basic salary plus capitation fees. Finally come the supplementary services to be provided for the most part by the local authorities and including child welfare, health visiting, home nursing, ambulance services and so on.

At the side of the Minister there is to be a Central Health Services Council of 41 members, of which 21 at least will be medical practitioners and the rest experts in various aspects of hospital and professional work. Some of the medical members are to be *ex officio* (e.g., Presidents of the Royal Colleges) and the rest appointed after consultation with professional and other bodies. The Council is to be advisory in function and will work partly through standing advisory committees.

The estimated annual total cost is put at £152 million, of which £32 million will come out of contributions to the new National Insurance Fund and about £10 million from rates levied by local authorities. The balance will be found from central funds raised by the ordinary methods of taxation.

Work among children, as already stated, has not been separately considered in detail. Hospital and specialist services will come under the new regional body; general practitioner work under the new local executive councils; child welfare and school medicine under local authorities and in this case there is some confusion because some relatively minor authorities have been allowed to retain their supervision of education under the new Education Act and the child health services will go with education.

The most obvious criticism which must now be apparent is the administrative complexity of the scheme. It would surely be better, it is argued, to put all health services under the new regional bodies, so as to avoid the chaos likely to arise when three or four authorities are dealing with an individual patient. But it will probably be answered that these regional bodies are too remote from the local government electors and not elected on a direct democratic basis. In any case, the exact composition of the new bodies is not stated in the bill and until this is known it is difficult to argue for giving them even greater power.

The transfer of hospital ownership has aroused a great outcry. The voluntary hospital spokesmen have used the phrase "mass murder," but this is the language of hyperbole and it is perhaps difficult for those who work at first class voluntary hospitals in London to realize the disadvantages under which these institutions have to exist in the country. The surveys of the hospital services of England and Wales that have been made in recent years have revealed a state of affairs which calls for radical reorganization. This is even more true of local authority hospital services outside a few enlightened areas such as those of the London County Council and Middlesex County Council.

Criticisms of the family practitioner service are mainly that the Health Centres, widely publicised, have not even reached the blueprint stage, and experimentation should precede the establishment of definite plans. The proposed control of the distribution of doctors, to be achieved in a sort of negative way, is still causing considerable concern, and this added to the abolition of the sale of practices (with compensation) is taken to mean a serious step towards a full-time state salaried service. The main professional bodies have proclaimed themselves sternly against this, and it is round this point that most criticism is likely to centre in the coming weeks. Private practice, alike for general practitioners and specialists, is to be allowed with certain safeguards, but it is freely suggested that the whole trend of the bill will be to abolish such private work in a relatively short time.

This is a brief outline of the bill and the main criticisms. If we can secure a Regional Board with adequate medical and university representation and get such a Board to take on more of the administration of the non-hospital services, then I believe we can make the new service work well for the sick of this country. But, as has been often said, it is a "medical service" rather than a "health service" as at present outlined. It will be for those who work it to give it the necessary twist to the preventive side.

ALAN MONCRIEFF, M.D., F.R.C.P.*

*Nuffield Professor of Child Health, Institute of Child Health, University of London.

News and Notes

MALIGNANT TUMORS OF INFANCY AND CHILDHOOD—ORGANIZATION OF A NEW CONSULTATION SERVICE

Announcement is made of the establishment of a consultation service to provide assistance in the diagnosis and treatment of tumors of infancy and childhood. This is a further step in the organization of a Children's Cancer Center, which is a unit of the new Medical Center for Children in Boston.

This is not a tumor registry. It is designed, rather, to give without charge, immediate diagnostic assistance and advice concerning therapy and prognosis, to any doctor who will send the necessary clinical data, microscopic sections, or x-rays. Replies will be given by air mail, or when necessary, by telephone, or telegraph. This project which is supported in part by a Grant-in-Aid from the National Advisory Cancer Council will be paralleled by a research program concerning the biology of tumors of early life, with a consideration also of the clinical, pathological, and epidemiological aspects of the problem.

The consultation service will be rendered by a group of three Pathologists, Dr. S. Burt Wolbach, Dr. Charles F. Branch, and Dr. Sidney Farber, and one Roentgenologist, Dr. Edward D. B. Neuhauser, with the cooperation, when indicated, of the entire staff of The Children's Hospital, through the Chiefs of the clinical services. Doctors representing all of the clinical and laboratory specialties concerned with the infant or child will be available for consultation.

Communications should be sent to Dr. Sidney Farber, The Children's Hospital, 300 Longwood Avenue, Boston 15, Mass., beginning Aug. 1, 1946.

FELS INSTITUTE'S PROGRAM AND FACILITIES EXPANDED

The Samuel S. Fels Fund of Philadelphia announces the erection of a new research laboratory building on the Antioch College Campus at Yellow Springs, Ohio. The new building, to cost about \$400,000, exclusive of equipment, is to house the activities of the Fels Research Institute. The Institute's program, devoted to the study of growth and development of children, is being expanded considerably in the following areas: Biochemistry with emphasis on blood and urinary enzymes, vitamin adequacy, ketosteroids, estrogens, and other hormones, in relation to growth progress and behavior; Genetics with emphasis on the inheritance of biochemical and physiological function patterns and growth patterns; Physiology with emphasis on resistance level to physical or emotional stress in relation to predisposition to psychosomatic disease and personality.

To house these activities and those of the Psychology and Physical Growth sections, physiological, physical growth, biochemical, and psychological laboratories, as well as office and library space, will be provided.

A new scientific advisory board has been created, consisting of Dr. Robert Yerkes, Yale, psychobiology; Dr. Ashley Welch, Cincinnati University, pediatrics; Dr. E. V. Cowdry, Washington University, anatomy; and Dr. Maurice Visscher, University of Minnesota, physiology. The Institute, established in 1929, is under the direction of Dr. L. W. Sontag.

Dr. Alvaro Aguiar of Rio de Janeiro, Brazil, has been elected President of the Brazilian Pediatric Society for 1946 and 1947.

The Pediatrician and the War

The following members have been released from service:

Dr. M. Bernard Brahdy, Mt. Vernon, N. Y.
Dr. Burtis B. Breeze, Rochester, N. Y.
Dr. Ward L. Chadwick, Denver, Colo
Dr. Edward J. Denenholz, Chicago, Ill.
Dr. Wilbur J. Fisher, Buffalo, N. Y.
Dr. Ellis H. Harris, Winnetka, Ill.
Dr. C. Jack Harrison, Chicago, Ill
Dr. Robert E. Jennings, East Orange, N. J
Dr. Daniel B. Landau, Hannibal, Mo.
Dr. Jacob J. Lichterman, Brooklyn, N. Y.
Dr. Joseph Palma, Honolulu, Hawaii
Dr. Sam Phillips, Little Rock, Ark.
Dr. John F. Sander, East Lansing, Mich.
Dr. James R. Sickler, Tucson, Ariz.

The following promotions have been reported:

Major Jack Chesney, Knoxville, Tenn., to Lieutenant Colonel
Captain W. V. B. Diering, Chicago, Ill., to Major

Book Reviews

The New-Born Infant: A Manual of Obstetrical Pediatrics. Emeison L. Stone, M D, ed. 3, Philadelphia, 1945, Lea & Febiger, 314 pages.

In reviewing this book by Dr. Stone, it must be remembered that, because the author is not primarily interested in pediatrics, the work will not live up to some pediatric ideals on such subjects as physiology and development of the newborn and infant feeding.

It does present, however, a common sense attitude toward the problems of newly born infants, and it is felt that it should be a part of the library of anyone interested in this most precarious period of human life. The material is interestingly written, and the information, for the most part, is accurate and well documented.

In evaluating the book, it would be fair to say that it forms a sort of missing link between pediatrics and obstetrics and that any such effort is decidedly worth while. If the pediatricians could know more about obstetrical problems and obstetricians know more about pediatric problems, both of these specialties would be better off.

C A A

Comment

A JOB FOR EVERY FELLOW

In last month's issue of the JOURNAL a new department was started: The Academy Study of Child Health Services. In the department this month Dr. Hubbard tells of some of the financial support the study has received. In addition to the \$18,000 contributed by the Academy to start the study and the large contributions of the United States Public Health Service and of the Children's Bureau in the way of personnel, gifts of money or staff have been made by the National Infantile Paralysis Foundation, the Field Foundation, and the Kellogg Foundation. Large contributions have also been made by a number of commercial corporations who are deeply interested in the health problems of infants and children and who recognize the leadership of the Academy in such matters. The huge sum of money which the two-year study will cost is in sight. This splendid financial support would not have been received were it not for the recognition that a sound factual basis is necessary for the development of intelligent planning for child health work in the future. Quite frankly, almost everyone is more or less fed up with the emotional and at times acrimonious discussion over health plans for children which has recently been taking place. This has been due in no small part to the discussions being based on opinion, or reflecting some social or political ideology. When the facts are found and made known it should be possible to formulate plans to meet the needs which will find support from all concerned.

Money alone will not make the study of value or a success. What is of equal importance is the wholehearted support the study is being given by the medical profession and by public and private child health agencies. Many state medical societies are already sponsoring and assisting the study which is being conducted at state levels. An editorial in the May 4 number of the *Journal of the American Medical Association* appeals to the entire medical profession to support and aid the study. We will not quote from this as it has probably been read by most Fellows. In the April 26 number of *Public Health Reports* an outline of the study was published calling for its support by all public health officers. It was stated in this article that the Academy has formally requested the support and assistance of all public health officials and the following comment was made: "This request, addressed by a national medical organization of high standing to governmental agencies, represents another milestone in cooperative action." So we find rallying to the support of the study not only money but the necessary technical and professional support which the study requires. We must not forget, however, that it is an undertaking and a responsibility of the Academy of Pediatrics. From the way the study is organized its success and value, in the ultimate analysis, will depend on the work and enthusiasm of the Fellowship.

The response on the part of the fifty-odd State Chairmen who will be responsible for much of the work has been splendid. They have accepted tremendous responsibility, but they cannot do it all. It will call for time and effort on the part of every individual Fellow. The pediatricians through their Academy have assumed leadership and they must not and will not fall down on the task which is the responsibility of every individual member.

It may eventually turn out that the Academy study, by pointing the way to united efforts to provide better health and medical care for the children of the United States, will help to solve the complicated and perplexing problems of adjustment between individual effort and public and private health agencies concerned with better medical care for all.

B. S. V.

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